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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

CHARLES RAGAN

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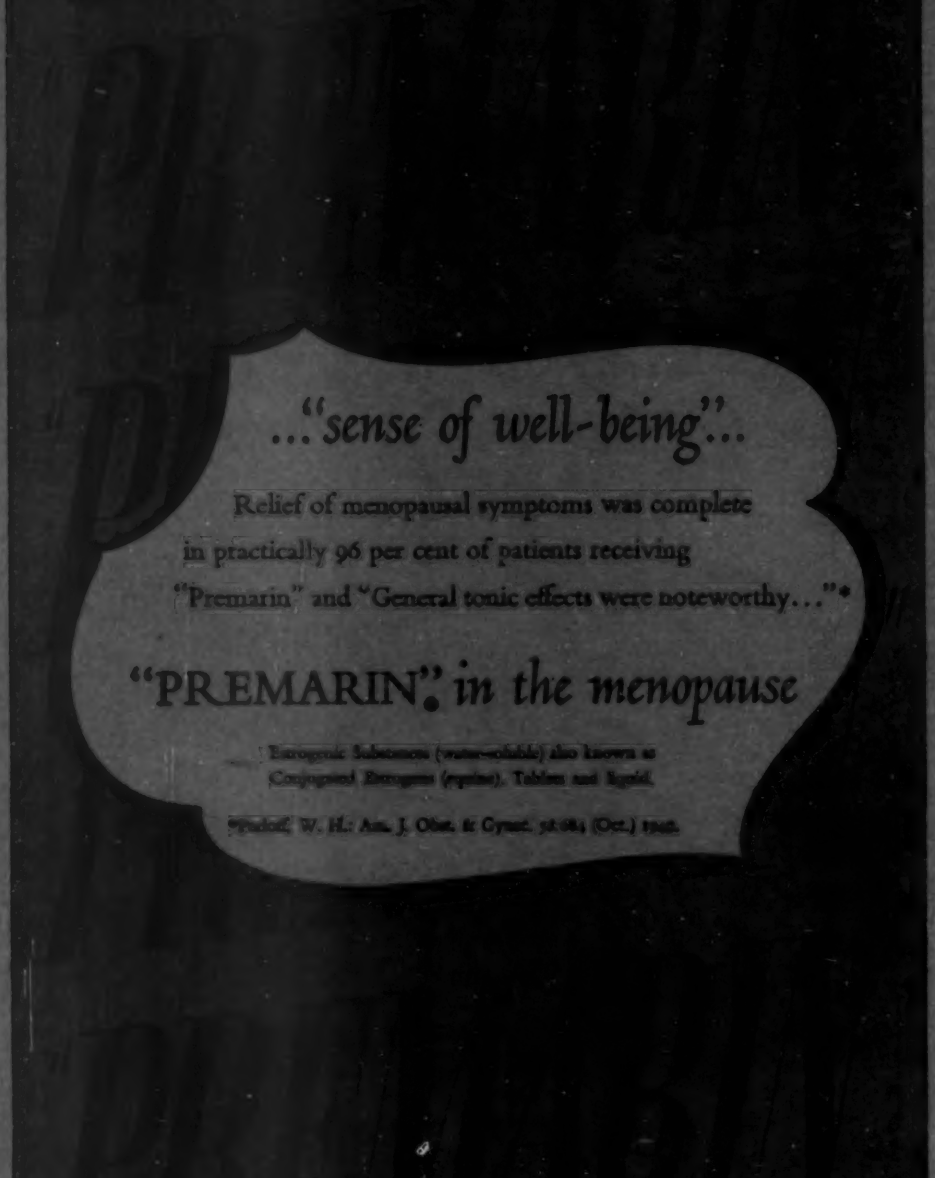
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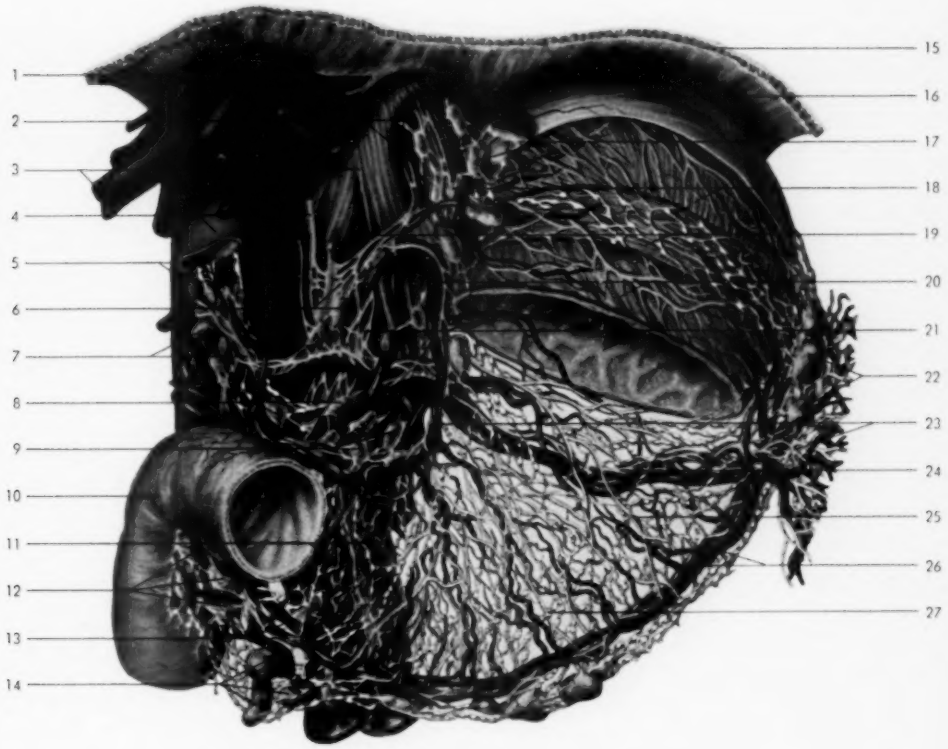

1 Middle and left hepatic veins
2 Right vagus nerve and esophagus
3 Right hepatic vein and crura of diaphragm
4 Inferior vena cava and greater splanchnic nerve
5 Portal vein and hepatic artery
6 Celiac plexus and celiac artery
7 Hepatic lymph node and hepatic rami of vagus nerve
8 Gastroduodenal artery and suprapyloric lymph nodes
9 Superior gastric lymph nodes
10 Duodenum
11 Superior mesenteric artery and vein
12 Subpyloric lymph nodes
13 Right gastroepiploic artery and vein
14 Inferior gastric lymph nodes
15 Diaphragm
16 Serosa
17 Paracardial lymph nodes
18 Left vagus nerve and longitudinal muscular layer
19 Abdominal aorta and circular muscular layer
20 Left gastric artery and oblique muscular layer
21 Celiac rami of vagus nerve and gastric mucosa
22 Splenic lymph nodes
23 Left gastric (coronary) vein and splenic rami of vagus nerve
24 Splenic artery and vein
25 Gastric rami of vagus nerve
26 Left gastroepiploic artery and vein
27 Gastric lymphatic plexus

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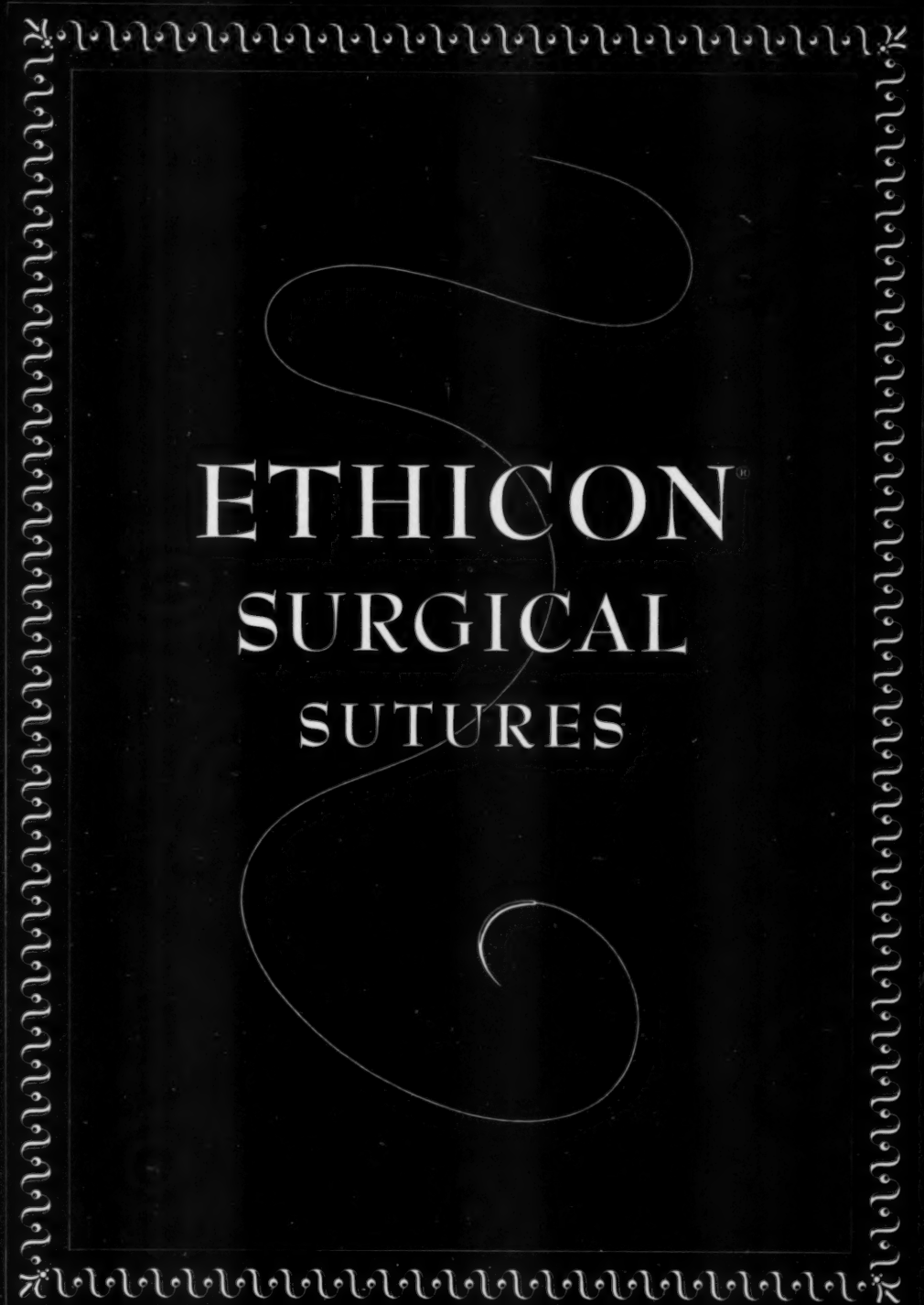
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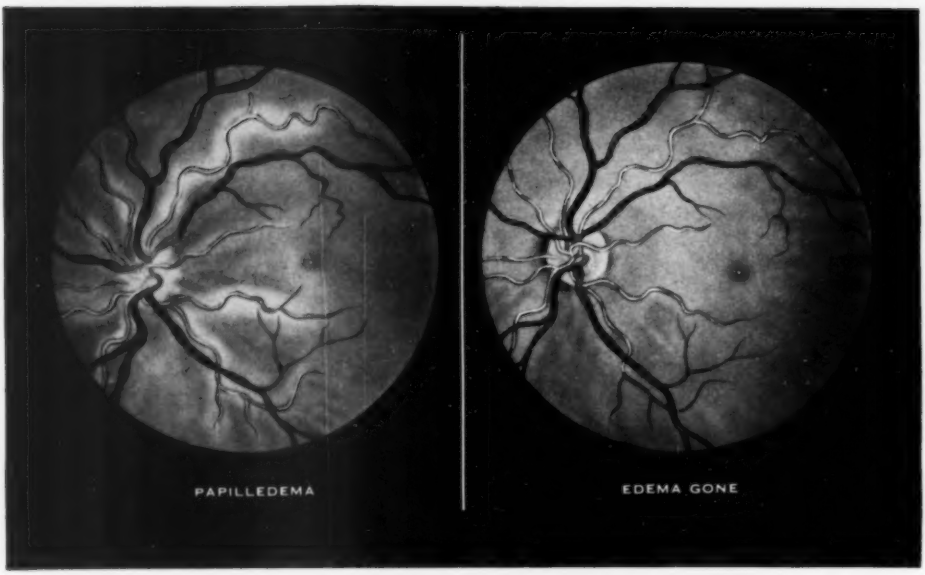
1. Rimmerman, A. B., and others: A Comparative Study of Sodium-free Salt Substitutes, Am. Pract. & Digest Treat. *2*: 168, 1951.
2. Fremont, R. E., and others: Postgrad. Med. *10*: 216, 1951.



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1. Grimson, K. S.; Orgain, E. S.; Rowe, C. R., and Sieber, H. A.: J.A.M.A. *149*:215 (May 17) 1952.
2. Paton, W. D. M., and Zaimis, E. J.: Pharm. Reviews *4*:219 (Sept.) 1952.

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1. Steinbrocker, O.; Berkowitz, S.; Ehrlich, M.; Elkind, M., and Carp, S.: Paper read before the Annual Meeting of the American Rheumatism Association, Chicago, Ill., June 6, 1952.

2. Kuzell, W. C.; Schaffarzick, R. W.; Brown, B., and Mankle, E. A.: J.A.M.A. *149*:729 (June 21) 1952.

3. Smith, C. H., and Kuna, H. G.: J. M. Soc. New Jersey *49*:306, 1952.

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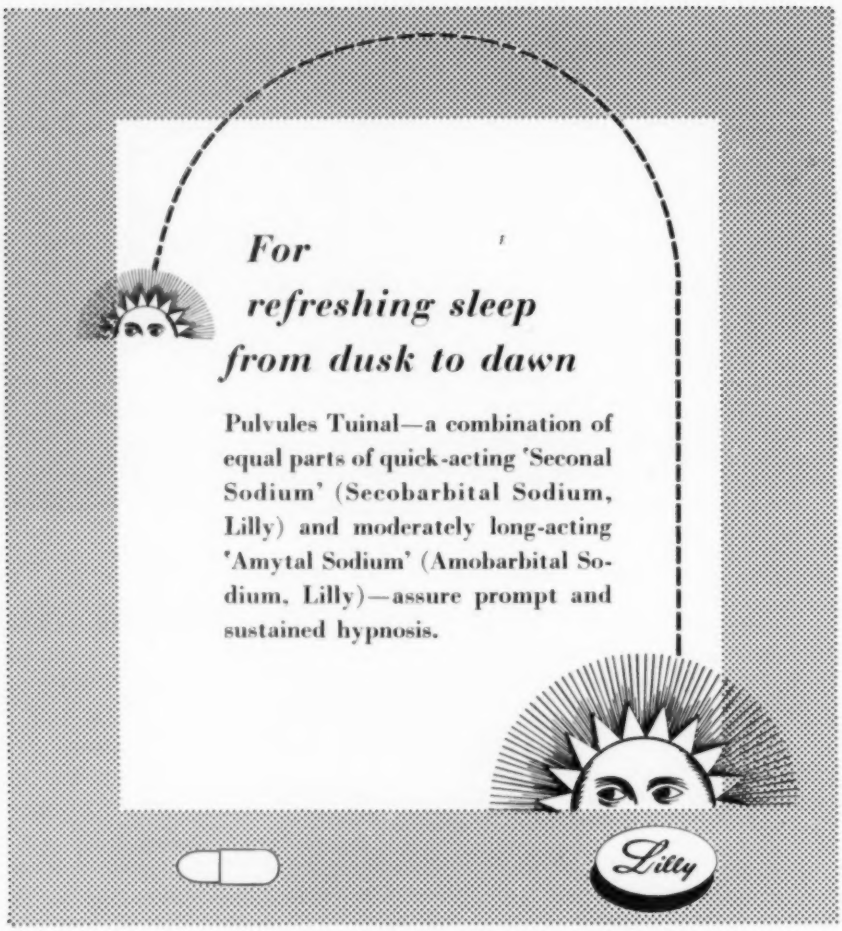
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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 29, NO. 5 MAY 1953

CORTICOTROPIN, CORTISONE AND RELATED STEROIDS IN CLINICAL MEDICINE: PRACTICAL CONSIDERATIONS*

CHARLES RAGAN

Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University

THE practical considerations involved in the use of a therapy may be developed from long clinical experience through trial and error or may be determined by experimental procedures which provide clues to the mechanisms involved. Our clinical experience in the use of corticotropin, cortisone and related steroids spans only three years, but we do have an understanding, covering several decades, of naturally occurring Cushing's syndrome which resembles the state induced by large amounts of these hormones. Experimental studies concerned with the mechanisms involved in the activity of these hormones have indicated that they have, among others, a marked antiphlogistic or anti-inflammatory action. The major part of this presentation will be related to the clinical application of this particular hormone action. The exact path-

* Presented at the 25th Graduate Fortnight of The New York Academy of Medicine, October 9, 1952. From the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York.
Supported in part by grant from the Masonic Foundation for Medical Research and Human Welfare. Cortisone supplied partly by Merck & Company, and partly from funds derived from the U.S.P.H.S. Research Grant No. A-21. Corticotropin supplied by Armour & Co. and Wilson & Co.

TABLE I—RESPONSIVE SYNDROMES
CLASSIFIED ACCORDING TO ETIOLOGY OF THE NOXIOUS STIMULUS

ESTABLISHED PHENOMENA OF SENSITIZATION

Asthma
Hay Fever
Urticaria
Contact Dermatitis
Hemolytic Anemia
Foreign Protein Reaction
Penicillin Reaction

SUSPECTED ELEMENT OF SENSITIZATION

"Collagen" Diseases
- Rheumatoid Arthritis
- Rheumatic Fever
- Lupus Erythematosus Disseminatus
- Periarteritis Nodosa
- Scleroderma
- Dermatomyositis

Thrombocytopenic Purpura
Multiple Sclerosis
Gout
Sarcoid
Uveitis

COMPLETELY UNKNOWN

Pemphigus
Regional Enteritis
Ulcerative Colitis

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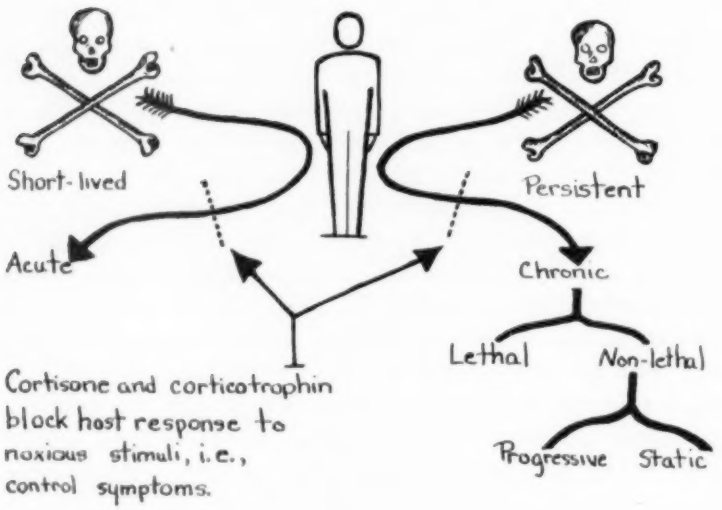
ways involved in this activity continue to be the subject of controversy but it seems safe to say that the hormones decelerate the response of the host to various forms of noxious stimuli; mechanical, chemical, infectious, those resulting from sensitization, or from tumor growth. No consistent evidence has been presented to show that an element of adrenal or pituitary functional deficiency exists in the diseases which respond favorably to their administration. It is probable that a beneficial antiphlogistic effect follows only upon excess adrenal function—hyperadrenocorticalism—which must be produced in some degree to modify the host response to noxious stimuli. It will be necessary in most of this discussion to speak in generalities and refer to patterns of disease, since

the large number and variety of responsive diseases precludes detailed discussion of each one.

Responsive Syndromes

1. *Etiology of the Noxious Stimulus:* Several clinical considerations should be mentioned before the practical aspects of this problem are discussed in order to limit the field of application. In many disease patterns, the response of the host to a stimulus is detrimental in the sense that the inflammatory process cannot be readily overcome and the processes of healing lead to deleterious host reactions as well, for example, as seen in rheumatoid arthritis. These syndromes in general are of unknown pathogenesis (Table I). The exceptions are those obviously related to established phenomena of sensitization such as the common allergies—asthma, hay fever and urticaria, contact dermatitis, certain hemolytic anemias, reactions to foreign proteins and reactions to drugs which have the characteristic pattern of foreign-protein-sensitization, such as penicillin. In other syndromes, the element of sensitization is under direct investigation and is suspected but is far from established. Falling into this category are the so-called "collagen" diseases, multiple sclerosis, many ophthalmological disorders, gout, sarcoid and possibly idiopathic thrombocytopenic purpura. In some, no clear concept of pathogenesis has been proposed and examples include various dermatological diseases and gastrointestinal disorders, such as regional enteritis or ulcerative colitis. In such phenomena of sensitization, an element of inflammation is present. A noxious agent, frequently a metal, may induce a detrimental host reaction; beryllium and gold are two such metals. The problems related to tumor growth are in another category and are discussed by Dr. Rawson. In the last subdivision of responsive syndromes are those related directly to well-defined hypo- or hyperfunction of the adrenals or the pituitary. These, as well, are the subject of detailed discussion in other parts of this Fortnight. We have chosen, therefore, to limit ourselves tonight to consideration of the control by these hormones of reactions damaging to the host, which, in the main, result from unknown noxious stimuli with an element of sensitization established in some, suspected in others, and absent in many. The characteristic feature of this particular type of noxious stimulus is the inability of the host to control it, and, in addition, attempts at control by the host lead to reactions which are detrimental. A disease is defined as being responsive

FIG. 1—HORMONAL MODIFICATION OF SYNDROMES CAUSED BY SHORT-LIVED OR PERSISTENT NOXIOUS STIMULI



to the action of these hormones when their action modifies beneficially a detrimental host response to a noxious stimulus.

2. *The Course of the Disease:* A second general point deserves consideration, namely, the distinction between a cyclic and a continuous disease (Fig. 1). This is of importance since, depending upon this characteristic, either intermittent or sustained therapy is indicated and the practical considerations of intermittent therapy are wholly different from those of sustained therapy.

3. *Prognosis:* The third and last generality to which I wish to call attention is the distinction between a lethal disease, a chronic progressive disease and a chronic static disease, since in each situation the need for avoidance of side-effects of hormone therapy varies. When faced with a potentially lethal disease, doses of hormones may be logically considered which would not be justifiable in a chronic static disease. One must, as well, realize that, in the latter, a slight beneficial effect obtained from

TABLE II—RESPONSIVE SYNDROMES CLASSIFIED ACCORDING TO COURSE AND PROGNOSIS

Acute			Thrombocytopenic Purpura Hemolytic Anemia Acute Gout Pollen Asthma Urticaria Foreign Protein Reaction Penicillin Reaction Exfoliative Dermatitis Due to Gold Acute Iritis and Uveitis Rheumatic Fever
Chronic	Potentially Fatal		Lupus Erythematosus Disseminatus Periarteritis Nodosa Pemphigus
	Non-Fatal	Progressive	Ulcerative Colitis Regional Enteritis Pulmonary Berylliosis Sarcoid Early Rheumatoid Arthritis Chronic Asthma Uveitis
		Static	Burnt-out Rheumatoid Arthritis Chronic Asthma

the hormone may be outweighed by the modification of the patient's adaptation to his chronic disease state.

AIMS OF THERAPY

So much for the theory and for the philosophy of treatment and we will now turn to the practical considerations in therapy. The first of these to be considered are the aims of therapy.

1. *In Acute Cyclic or Self-Limited Disorders:* In acute cyclic disease (Table II), one wishes to modify the host response during a temporary period of crisis. A dramatic example of this is seen in acute gout, which has become refractory to colchicine. The impression has been circulated that colchicine refractoriness may be overcome by the administration of one to two injections of corticotropin concomitant with colchicine, but in many instances, this has not been the case. In most patients, a

week of corticotropin has been required for control and acute gout has not followed withdrawal. Another example of the acute cyclic process is seen in the treatment of idiopathic thrombocytopenic purpura by cortisone or corticotropin. Bleeding often ceases before a rise in platelets ensues and in many instances, after ten days of therapy, a platelet rise has appeared which may well persist following withdrawal of the hormone.[1-3] The patient is a better operative risk for splenectomy when not bleeding profusely. The same reasoning and therapeutic approach applies, also, to the treatment of acute hemolytic anemia. Frequently in both idiopathic thrombocytopenic purpura and in an acute hemolytic crisis, a splenectomy may not be required since a remission may continue following hormone withdrawal.

Disease patterns resulting from sensitization in which the patient may be freed from contact with the sensitizing substance afford an example of the effective use of these hormones; for example, pollen asthma where the pollen source can be eliminated, sensitization to foreign protein (therapeutic sera such as tetanus antitoxin), sensitization to penicillin, gold reactions and the aplastic blood response to certain noxious agents. Our experience with the latter has been limited but we have one patient who developed an aplastic response presumably to either irradiation or one of the sulfonamides who, after eleven months of cortisone administration, maintained his improvement when cortisone was withdrawn. Therefore, during an acute cyclic episode or in a situation where the noxious stimulus may be removed or its action is spontaneously dissipated in time, the aim is to suppress the host response only during the time of activity.

2. *In Rheumatic Fever:* There are two major aims in the treatment of rheumatic fever. The first is to avoid a fatal outcome during the acute phase of the disease, the second being the prevention of rheumatic heart disease. The most careful study concerning the value of cortisone and corticotropin in the treatment of the acute phase of rheumatic fever has been the cooperative effort conducted in this country, England and Canada under the auspices of the Medical Research Council of England and the United States Public Health Service.[4] This well controlled study has been the subject of a preliminary report dealing with the acute phase of the disease, but it is too early for the follow-up. The report indicates that acute rheumatic activity responds equally well to salicylates, corticotropin or cortisone. This study may be criticized as a

statistical one, concerned with the response of mild rheumatic fever to the administration of salicylate, corticotropin and cortisone, since the severity of the disease could not be assessed fairly under the conditions established. At the Presbyterian Hospital, we have been among the strongest proponents of the value of salicylates, in adequate amounts and for adequate periods of time in the treatment of rheumatic fever. No doubt exists, however, that the hormones are more potent anti-inflammatory agents than the salicylates, but there is also no question but that the hormones, being more potent, can have more toxic effects. It seems probable that, in the future, the use of corticotropin and cortisone in rheumatic fever will be limited to those patients with severe disease who have failed to respond to the administration of salicylate.

The second aim in the treatment of rheumatic fever, as already stated, is the prevention of rheumatic heart disease. Collection of data in the cooperative study is being continued and a report on this second phase of the study will ultimately be forthcoming. Three factors, however, must be considered which might lead to a pessimistic viewpoint concerning our ability to wipe out rheumatic heart disease by the hormone treatment of acute rheumatic fever. The first is that many patients with rheumatic heart disease—one-third to one-half—have never had a known acute attack of rheumatic fever which could be treated. The second factor is related to the time lag between onset of inflammation and the application of an anti-inflammatory agent. In the interval, the inflammatory process develops and, when decelerated by the anti-inflammatory agent, is replaced by a repair process with scar formation leading to the cardiac stigmata of rheumatic heart disease. The third factor is that in some instances the inflammation will be so marked and such large doses of the anti-inflammatory agent will be required to decelerate the inflammation, that vital processes will be affected and some degree of inflammation must of necessity persist if life is to continue. Thus, there is little likelihood that rheumatic heart disease can be eradicated by the *treatment* of acute rheumatic fever. Hope would appear to lie primarily in the direction of the *prevention* of acute rheumatic fever.

3. *In Chronic Disease States:* The aims of treatment in the sustained therapy of chronic disease naturally vary with the type of disease under treatment. A cure by eradication of the disease process is the ultimate goal but in the diseases under discussion, this has not been achieved. It

is a reasonably safe generalization to state that the hormones cure nothing, but simply control symptoms. Short of a cure, however, much can be done and in all instances, the comfort of the patient—palliation—is of major importance. In lethal diseases such as lupus erythematosus disseminatus, periarteritis nodosa, pemphigus, or the leukemias, one wishes to control unpleasant symptoms even though one cannot prevent the ultimate fatal outcome. Under these circumstances, it is legitimate to take certain risks with hormonal overdosage, keeping in mind the aims of palliation and of the postponement of a lethal outcome.

In chronic progressive disease, and most of our experience in this sphere has been with early progressive rheumatoid arthritis, the practical aim is to slow down the progression of the disease in the hope that the disease will abate over a period of time. In rheumatoid arthritis, one wishes to minimize deformities, afford palliation, and provide the patient some measure of comfort. In addition to hormone therapy, other modalities of therapy should be employed to attempt to modify the disease. Hormonal treatment *alone* still constitutes an experimental approach. It is to be considered an adjunct to therapy and should not be regarded as complete therapy. Although our therapeutic hope in rheumatoid arthritis has been the control and termination of the disease, we have not been able to achieve the latter. We have, however, been able to slow the rapid progress of the disease, allow more function and provide considerably more comfort. In multiple sclerosis, a similar trend has been reported.

In a chronic static disease, we have found from bitter experience that we have not been able to overcome defects which have been of long duration and consequently have been unable to change a bedridden invalid of years standing into a normally functioning individual. We have, therefore, lowered our sights and set them at palliation alone. Palliation may be considered functional and economic rehabilitation to a certain extent, for, when pain is decreased and comfort increased, the patient may carry out more of his daily activities including some which may be of economic importance, but many which are of importance to his sense of social well-being. A patient with a severe crippling disease who can fend for himself a small bit more than before treatment has, in his own mind, made a definite advance. This small bit may be insignificant to the physician but to many patients makes the difference between misery and some enjoyment of life.

Treatment should be long continued in this type of situation. It is not to the advantage of the average patient with a chronic continuing disease to receive the hormone for a period of ten days and then stop. One should anticipate sustained therapy. If treatment is stopped, the patient has not only lost his adaptation to a chronic disease state, but there is a very real possibility that following withdrawal of the hormone for a variable period of time, the disease may be more active than during the pretreatment period.[5] A point of practical importance is the cost of therapy. A patient requiring 75 mgm. of oral cortisone daily at present prices must spend $1.20 a day for medication alone, to which must be added doctor's fees and fees for laboratory procedures totalling a not inconsiderable amount. It is unwise for the patient with a chronic static disease to mortgage himself for the price of the hormone, as this obviously leads to further difficulties, and unless these costs can be met with relative ease, hormone therapy should not be instituted.

In these chronic diseases, both progressive and static, that ephemeral miasma known as the activity of the disease apparently determines the dosage of hormone required for control. It, therefore, follows that in a disease with great activity, more hormone will be required for minimal palliation, and will lead to a greater incidence of side-effects. Since the appearance of side-effects determines the ability of the patient to continue on hormonal therapy, a smaller number of patients with severe disease will be able to continue. This feature, the apparently direct relationship between dosage of hormone and incidence of most untoward effects has awakened us to the realization that a complete symptomatic remission is not to be desired, since smaller doses of hormone provide some benefit with a greater possibility that therapy may be continued. Patients with severe progressive disease requiring large amounts of hormone have in general developed more complications than others, and maintenance of such patients has not been easy. As a corollary to this, patients with mild disease treated suboptimally with small doses of hormone have not presented too major a problem. The challenge rests in the fact that the mild disease has done reasonably well on many forms of therapy whereas the severe has not, and one wishes to do all that is possible for the latter. Palliation—chiefly pain relief—for the patient with mild disease with these hormones in small doses seems completely feasible. Treatment of the patient with severe disease with larger amounts of hormone presents difficulties which must be met. To meet these, it is

important to continue treatment despite the appearance of minor side-effects. In chronic disease, the aim of therapy, therefore, is modified by the nature of the disease. Three general types have been discussed, the potentially lethal where the postponement of death is important, the chronic progressive where a deceleration of the process is hoped for, and the chronic static disease where palliation is the goal. A sustained program of therapy is of great importance and before instituting therapy, its cost should be considered.

Physiological "Side-Effects"

The physiological effects of the hormones which are not directly related to a specific anti-inflammatory action on the disease under treatment are commonly known as "the side-effects." If one starts with the premise that, to produce a beneficial effect, some measure of hyperadrenocorticalism must be induced, a knowledge derived from the natural history of spontaneous Cushing's syndrome might afford helpful information concerning expected eventualities. This syndrome will be discussed in detail by Dr. Knowlton. Most of the physiological effects encountered in iatrogenic Cushing's syndrome are related to the size of dose of hormone administered and the duration of its administration. In acute short term treatment in which a large dose of hormone is employed, one may foresee the possible development of sodium and water retention, hypokalemia, mental aberrations, and interference with carbohydrate tolerance. When one is confronted with an acute disease, perhaps lethal in nature, the dose of hormone need not be limited because of the possibility of these severe side-effects. In most such instances, with the notable exception of the mental changes, complications of therapy subside promptly when hormone is withdrawn.

When faced with sustained therapy the problem is wholly different. If the disease is not likely to have a lethal outcome and the aim is the control of symptoms, the avoidance of overdosage is obviously of considerable moment. A suboptimal dose of hormone has been advocated under these circumstances whereby a beneficial effect is obtained but the symptoms of hyperadrenocorticalism are minimized. If, however, the disease is of a lethal nature, enough hormone must be given to control symptoms, and side-effects are of minor importance even when sustained therapy is indicated. The physiological hormonal effects to be anticipated in sustained therapy may be compared to the clinical picture

TABLE III—A COMPARISON OF FINDINGS IN SPONTANEOUS CUSHING'S AND LONG-TERM CORTISONE-ACTH ADMINISTRATION

Symptoms or Signs	*Incidence in spontaneous Cushing's syndrome. 222 cases* (%)	*Incidence in long-term cortisone-ACTH therapy. Average duration 14.8 mos. 100 cases* (%)	*Incidence in high-dose* therapy. 69 cases* (%)	*Incidence in low-dose** therapy. 31 cases* (%)
"Cushing" obesity	97	85	84	85
Hypertension or elevation of blood pressure	85	24	25	18
Menstrual disturbance or impotence in men	75	20	19	21
Hirsutism in females	70	40	39	42
Striae	68	3	3	3
Plethoric appearance	60	23	23	21
Weakness and backache	58	36	44	28
Mental symptoms	40	36	35	41
Headache	39	8	7	11
Acne, pigmentation or other rash	37	15	13	20
Ankle edema	35	45	46	44
Poor wound healing or unusual infection	33	32	39	26
Purpura or easy bruisability	30	7	10	0
Polydipsia or polyuria	28	4	6	0
Glycosuria	27	6	3	10
Exophthalmos	7	0	0	0
Virilism	6	0	0	0

OTHERS: Osteoporosis, peptic ulcer, spontaneous seizures.

* 525 mgm. cortisone/wk. or over; 210 mgm. ACTH/wk. or over.
** up to 525 mgm. cortisone/wk. or 210 mgm. ACTH/wk.

of naturally occurring Cushing's syndrome. The data that Knowlton and Plotz[6] have obtained in a large series of patients may be compared with the side effects seen in patients treated with hormone over a period of time (Table III). These side-effects include those seen during acute therapy and, in addition, others related to the time element involved in prolonged therapy: retention of salt and water with the onset of congestive heart failure; in rare instances, the development of a low serum potassium with muscle weakness; a trend toward hypertension; in a certain number of patients depression of thyroid function and, in most patients, the physical stigmata of Cushing's syndrome, such as hirsutism, acne, rounding of the face, buffalo hump and striae. Mental aberrations

are seen as well. There is a possibility that there may be an increased incidence of thromboembolic phenomena during hormonal administration and in the withdrawal period. In our experience with rheumatoid arthritis, the incidence of thromboembolic phenomena has not increased since the introduction of therapy with cortisone and corticotropin, and indeed some question remains whether or not an hypercoagulable state is induced by their administration.[7] Many patients show a decreased tolerance for carbohydrate, during hormone administration, but this achieves clinical importance in relatively few. One should, however, be aware of this potential and be alert for its appearance.

Whereas an anti-inflammatory action is the desirable end to be achieved in the disease states under discussion, this effect may prove deleterious to the host under certain circumstances when it may be looked upon as another side-effect. It must be remembered that the anti-inflammatory action involves all tissues of the body during systemic administration, modifying not only the inflammation related to the disease under treatment, but coincidental inflammatory processes which might be adversely affected. For example, a pyogenic infection which might be expected to localize spontaneously may be transformed into a diffuse systemic infection through the anti-inflammatory effect of the hormone. The most common clinical patterns encountered have been activation of latent pulmonary or other tuberculous infection; masking of a peptic ulcer whereby symptoms of perforation have been minimal and attended by few clinical signs; the modification of abdominal crises, as that following perforation of a viscus or a localized collection of inflammatory cells (acute appendicitis); and, in rare instances, the modification of the host response to pneumonia whereby the patient succumbs to an overwhelming infection without clinical evidence of its presence.[8] Masking of this type is seen infrequently during short-term therapy at high dosage levels but more frequently during sustained suboptimal dose therapy and constitutes the main hazard in the latter. Possibly related to the antiphlogistic action of these hormones has been the rather frequent appearance of a peptic ulcer in our group of hormonally treated patients with rheumatoid arthritis. We have seen thirteen instances of peptic ulcer among eighty patients. Unfortunately we have no comparable control data on non-hormonally treated patients with rheumatoid arthritis. Bauer's figures would indicate that the incidence was much lower than this in the pre-hormone era.[9] The high incidence

in our series may result from our special efforts to search for a peptic ulcer. One should mention, also, that the incidence in our group has been much greater than that observed in other centers throughout the country.

A final problem is posed by the increase of osteoporosis, which is difficult to evaluate. In most instances of Cushing's syndrome, osteoporosis is present, but in many patients requiring hormone therapy, osteoporosis has existed before hormonal administration. Indices of progression of osteoporosis are difficult to obtain since techniques of roentgen examination are usually quantitatively inaccurate. In most balance studies where both fecal and urine calcium and phosphorus have been measured, the patient has been in negative balance for these minerals during the administration of large amounts of hormone.[10] However, in clinical practice conclusive evidence for the progression of osteoporosis in patients with rheumatoid arthritis has been the development of spontaneous fractures, which were notably infrequent in these osteoporotic individuals before the advent of cortisone and corticotropin.[11] We have seen spontaneously occurring fractures in patients with rheumatoid arthritis on sustained moderate dosage, i.e., suboptimal therapy, only in those individuals with physical inactivity, such as a wheelchair or bed existence, or in the post-menopausal period.[12] On the other hand, we have seen such fractures in patients who were neither post-menopausal nor bedridden when large amounts of hormone have been given for long periods of time (200 or more mgm. of cortisone daily for a year). We have also suggestive but not conclusive evidence that there has been a decrease in density of the dental lamina dura during sustained suboptimal administration. If this is substantiated, it would support the contention that osteoporosis is induced even at suboptimal dosage levels in an ambulatory, premenopausal patient. In summary, it may be reemphasized that some degree of hyperadrenocorticalism is required to produce an anti-inflammatory hormonal action, which leads to a clinical picture similar to Cushing's syndrome. The degree of Cushing's syndrome produced is dependent upon the size of the dose of hormone and upon the duration of hormone treatment. In acute, short-term treatment, side-effects are of little importance and during the treatment of a potentially lethal disease, their importance is negated by the possible fatal outcome. When the disease is seldom lethal, their importance is great and the dose of hormone must be kept as low as feasible to achieve

some benefit. The stigmata of Cushing's syndrome classically described have led to relatively little real difficulty but the total anti-inflammatory action of the hormones has been our major concern. Specific side-effects which have been particularly troublesome during sustained therapy have been masking of common inflammations, reactivation of infections, the development of peptic ulcers and the progression of osteoporosis. Congestive failure, carbohydrate intolerance, hypokalemia and the development of hypertension have to date not presented great difficulty.

Management of Untoward Side-Effects: The management of side-effects has two facets. The first is their avoidance if at all possible and, secondly, the control of those that develop. Small doses of hormone and short periods of administration will minimize side-effects. When neither course is feasible, the side-effects mentioned above may be anticipated. Prophylactically, a patient's weight should be followed carefully and most patients should be asked to forego their salt shaker. With the appearance of edema or a sharp weight gain, sodium restriction should be increased by the conventional low sodium diet. In certain critical situations, a strict low sodium diet may be needed, including salt-free bread and the avoidance of all salt in cooking. Mercurial diuretics may be used and, in a few patients, continuing use may be indicated. It should be stressed that when mercurials are used, the excretion of potassium in the urine is increased and under these circumstances a low serum potassium with its attendant difficulties may be encountered. Hence, when mercurial diuretics are used over a long period, supplemental potassium in the form of 2 to 3 grams of enteric-coated potassium chloride daily should be taken by mouth. If it is not feasible to follow the serum potassium at one or two monthly intervals, oral potassium chloride should be added even when mercurials are not being used if the average daily dose exceeds 75 mgm. of cortisone or 40 I.U. of corticotropin daily.

Intolerance for carbohydrate of mild degree as manifested by an abnormal glucose tolerance curve or occasional glycosuria is commonly seen during the administration of these hormones. When this reaches the degree of persistent glycosuria with a markedly elevated fasting blood sugar, diet restriction of carbohydrate and calories will often be all that is needed. If the diabetic features persist, insulin may be required but when this becomes necessary, a careful reevaluation of the need for hormone therapy is indicated. The use of insulin, diet restriction and

cortisone poses a difficult therapeutic program which should be undertaken only in the face of an urgent need for hormone.

In certain individuals—less than 5 per cent of the total in our group on sustained therapy—a depression of thyroid function has appeared during the administration of cortisone or corticotropin. This is manifested by a decreased radioactive iodine uptake. Presumably the hormones are calorigenic and a normal BMR persists despite lowered thyroid function although overt myxedema has not been seen. Early in the use of the hormones, the claims made that 1 to 2 grains of thyroid extract daily would permit a better effect have not been confirmed. In our experience, the addition of thyroid extract to the therapy is seldom if ever warranted. When hormone is withdrawn, thyroid function promptly returns to normal.

When a major thromboembolic episode ensues (by this is meant infarction and not a peripheral thrombophlebitis without infarction), unless the continuation of hormone administration is a question of life or death, we have withdrawn it. In the presence of peripheral thrombophlebitis alone, our practice has been to hospitalize the patient, continue suboptimal hormone administration and employ heparin anticoagulation. There is suggestive evidence to indicate that dicumarol anticoagulation does not overcome the presumed hypercoagulable state induced by the hormones.[7]

As outlined above, the detection of osteoporosis has depended upon the development of spontaneous fractures. When these have appeared, we have in most instances withdrawn hormone with the simultaneous administration of corticotropin. However, in certain critical situations, we have continued the hormone and have added estrogens, testosterone, a high calcium intake and strontium lactate. This presents a formidable therapeutic undertaking but in a potentially lethal situation may be warranted. We have one patient who on such a regimen has clinically developed a firm union of her fracture sites but no callus or evidence of union by x-ray. Prevention of the development of osteoporosis by the prophylactic administration of testosterone has not been practicable since large amounts of testosterone—enough to produce marked masculinization—have been required to overcome the negative calcium balance.[13] Studies concerning the value of the administration of strontium with cortisone are now in progress.[14]

Mental aberrations have been seen not infrequently in Cushing's

syndrome and, as stated before, appear in induced hyperadrenalism as well. These may take many forms and their pathogenesis is not clearly understood. By some, they are believed to be release phenomena, by others a manifestation of an underlying potential. Manic-depressive, schizophrenic and organic psychoses, as well as marked anxiety states, and also such relatively simple phenomena as intolerable insomnia have been described. In all, with time, when hormone is withdrawn, a "normal" psychic state has returned. In some, the psychosis has been so acute as to be potentially lethal, and under these circumstances we have resorted to electroshock therapy with improvement. None of these abnormal reactions has been permanent, but a patient who develops a psychotic reaction on the hormone has a greater than even chance of subsequently developing one if hormone is again administered. We feel a severe psychic reaction is a definitive indication for withdrawal of this type of therapy and that it should not be resumed. Withdrawal of cortisone should be undertaken with simultaneous administration of corticotropin in a psychiatric hospital under careful observation, particularly if suicidal tendencies are present. We have been unable to predict the induction of a psychosis, but have seen them much less frequently in the last year and are unable to explain this decline in incidence.

When a localized or systemic infection appears in patients receiving hormonal therapy, it should be treated by conventional means. When possible, severe infections should be treated in the euadrenal rather than the hyperadrenal state and therefore withdrawal of cortisone with corticotropin is advisable. If withdrawal in itself is deemed hazardous, then, of necessity, cortisone must be continued, preferably with corticotropin and suitable antibiotics and/or surgery as needed. It is often advisable to decrease the dose of hormone to permit some clinical evaluation of the situation, as well as to allow a host response which is necessary for the healing of most infectious processes. When large doses of hormone are used—more than 100 mgm. of cortisone daily—delay in repair processes induced by these hormones assumes clinical importance in open granulating wounds such as wounds with loss of substance, and in wounds with gut anastomoses. Skin incisions with primary closure have usually healed adequately in patients receiving up to 100 mgm. of cortisone daily with only slight delay which may be overcome by leaving the sutures in situ a longer time than usual. If untoward events arise during cortisone treatment, corticotropin should be administered as

well, so that sudden withdrawal may be carried out if indicated. This has been our policy and, after five days of intramuscular corticotropin in gelatin, the cortisone has been stopped and the patient has been maintained through the crisis on corticotropin alone. The latter may be withdrawn suddenly with relatively little danger during a period of strain.

Injection abscesses—a seemingly minor difficulty—may assume alarming proportions during hormone administration. The frequency with which these appear may be decreased by careful aseptic injection techniques but even in the best hands, abscesses have developed. When these appear, associated with the masking anti-inflammatory action of the hormones, the abscess may reach astounding proportions without a great deal of pain. The patient may not be disturbed by an abscess from which 100 cc. or more of pus may be drained. Rarely, these abscesses may be treated locally by aspiration and with the use of local and systemic antibiotics, but in most instances, open surgical drainage has been required. In order to assure adequate filling in with granulations, hormone dosage should be decreased to 50 mgm. of cortisone, or less, daily. In practice, in most instances, we have been forced to withdraw the hormone completely with corticotropin as outlined below.

Indications for Withdrawal: It must be stressed, as mentioned above, that the withdrawal of corticotropin and particularly of cortisone after prolonged periods of therapy should not be undertaken without trepidation. The indications for the termination of hormone therapy which we have adopted are several and may be considered here. In general, they represent severe and dangerous characteristics of Cushing's syndrome, and include overwhelming infections which cannot be controlled by antibiotics, all tuberculous infections or ones suspected of being tuberculous, bleeding peptic ulcers, resistant diabetes not readily controlled by diet and insulin, major thromboembolic phenomena, congestive heart failure refractory to the usual measures of treatment, severe mental disturbances, and abdominal crises such as suspected perforation of a viscus or peritoneal infection. We are of the opinion that the hormone should not be withdrawn solely because of the appearance of the stigmata of Cushing's syndrome, or because of mild congestive failure, minor infections, hypokalemia correctable by oral potassium, mild glycosuria controlled by diet or the development of mild hypertension.

The dose of hormone needs to be changed frequently, titrating the dose against symptoms so that, in remittent chronic disease such as

rheumatoid arthritis if a remission be anticipated, the hormone may gradually be withdrawn. Tapering of the hormone dosage during withdrawal is of value only under these circumstances. When a patient continues in a fair remission on 25 mgm. of oral cortisone daily, it has been our policy to withdraw the hormone—under the schedule to be outlined later, with the hope that a spontaneous remission may ensue. When symptoms have recurred on decreasing the dose, we have seen no advantage in such tapering.

No absolute criteria can be set down regarding the time to withdraw the hormones, but as in all clinical medicine, advantages must be weighed against disadvantages. If the indications for continuing hormone administration are imperative, we have continued it even following the development of spontaneous fractures, and have added testosterone, estrogen and strontium lactate to our therapeutic regimen. This obviously represents a desperate course but in some circumstances in which these hormones are used, desperation is real. The point which I wish to emphasize is that withdrawal should not be undertaken lightly and withdrawal for minor reasons should be avoided. If, following withdrawal, the inflammatory process for which the hormone was given increases in intensity, an increase of anti-inflammatory hormone action will be required for control, i.e., more hormone will be needed. In other words, mild disease activity may be transformed into severe in the withdrawal period and may persist as severe for a considerable period of time.

Choice of Hormone Preparation

One very practical consideration revolves about the choice of hormone to be used. In general, one has available three preparations: cortisone acetate (compound E), corticotropin (ACTH) and hydrocortisone acetate (compound F). The pregnenolones have been of no value and have been abandoned as essentially inert. Desoxycorticosterone with ascorbic acid has proved worthless. Other adrenal hormones such as corticosterone and compound A have been shown to have little or no anti-inflammatory action. For all practical purposes, cortisone and compound F are similar when given systemically, although quantitative differences in activity have been described in acute experiments.[15] There is a clinical impression that acute gout responds more satisfactorily to corticotropin than to cortisone but during sustained long term therapy, our patients with other diseases have reacted in the same fashion to

cortisone or corticotropin with one significant difference: cortisone administration leads to a suppression of endogenous adrenal function, which in all instances has returned in time after withdrawal. Oral cortisone is the simplest form, since injection difficulties, such as abscesses, are avoided. Injectable cortisone requires a large volume and at the onset has a slow effect which persists after withdrawal. Intramuscular corticotropin in a gelatin menstruum can be administered satisfactorily every twelve to forty-eight hours, although the problem of continuing injections remains and lumps have frequently developed at the injection site. Intravenous corticotropin is the method of choice for a rapid emergency. It is simple, but in our hands has not been practical for sustained therapy. A point deserving of emphasis is that during the withdrawal of cortisone, one should administer corticotropin as well. Although, with very few exceptions, no overt evidence of adrenal insufficiency has been seen in the withdrawal period, patients have responded less well to strain than when euadrenal. The adrenal unresponsiveness to corticotropin which has been used as an index of adrenal atrophy has persisted for as long as three to ten days, the longest period, following withdrawal of intramuscular cortisone. Adrenal unresponsiveness of this type may be abolished by the administration of corticotropin with cortisone. Engleman[16] has shown that if corticotropin is given daily intravenously in a slow infusion (25 mgm. in 500 cc. of dextrose and water over a period of five to six hours) an adrenal response has appeared after three days, regardless of the amount or duration of cortisone therapy. We feel that withdrawal of cortisone should never be undertaken without the administration of corticotropin during the last few days of cortisone administration. This is particularly important during periods of strain as during surgery or an infection when cortisone withdrawal may be indicated. Intravenous corticotropin apparently achieves a more rapid effect than intramuscular but if necessary the intramuscular route in the form of a gelatin preparation may be used for a period of four to five days.

The use of compound F (hydrocortisone acetate) has been confined chiefly to intra-articular use.[17] Cortisone acetate and its free alcohol have a variable effect when given intra-articularly and frequently are more irritating than not, whereas the effect of hydrocortisone acetate is quite uniformly beneficial to the patient. In rheumatoid arthritis, oftentimes many joints are involved and the practicality of multiple

intra-articular injections is questionable. When one joint persists, however, in spite of other therapy, administration of this hormone intra-articularly in doses of 25 to 50 mgm. (not sufficient to affect the patient systemically) has been followed in most instances by marked symptomatic improvement. In this disease, the short duration of the relief obtained—four to seven days—has been a disturbing feature and presents a difficult problem in practical therapy since intra-articular injections must be given at weekly intervals. In degenerative joint disease, this approach has apparently been more practical since frequently symptoms are monarticular, and the beneficial effect which is real usually lasts for a longer time. In many instances one or two injections at weekly intervals have been followed by what one might almost call permanent improvement since for the period of observation (up to six months) no further injections have been necessary. The administration of this hormone intra-articularly may be carried out with relative ease. Experience in intra-articular injections can be gained readily by visiting one of several arthritis clinics in the city, and, if ordinary sterile precautions are taken, notably keeping one's hands away from the site and away from the instruments involved, no untoward reactions should be anticipated.

Summary and Conclusions

The use of cortisone and corticotropin in practical therapy requires an understanding of the current concepts of the mode of action of these hormones as anti-inflammatory agents. An understanding is required as well as of the nature of the disease to be treated, its course and prognosis. The physiologic effects of the hormones other than the specific anti-inflammatory effect on the process under treatment, known as the "side-effects" are dependent upon two factors, the size of the dose of hormone and the duration of treatment. The physiologic effects are similar to the symptoms of Cushing's syndrome, a potentially lethal disease, and subside quite promptly when hormone is withdrawn. For these reasons, side-effects are of less importance in short-term therapy and may usually be minimized. In long-term therapy, particularly in a non-lethal disease, we are forced to consider them as of paramount importance and to moderate the beneficial effect of the hormones by decreasing the dosage—suboptimal therapy.

In a chronic disease state, one must plan on continued hormonal ad-

ministration with the ever-present but frankly dim hope that the disease may abate, at which time the hormone may be withdrawn. The continuity of hormone administration predicates that the patient must be able to afford the cost, and be free of lesions which might be intensified by the prolonged induction of a mild hyperadrenal state, such as tuberculosis, hypertension, diabetes mellitus, poor cardiac function, and possibly severe mental breaks in the past. We do not feel that a history of a peptic ulcer forms a contraindication. The patient must be advised that complete symptomatic relief will not be sought and a certain amount of discomfort will be allowed to remain during treatment. Extreme vigilance must be maintained by the physician with a constant awareness on his part that a major action of these hormones is their masking one on inflammatory reactions of all kinds. Constant attempts should be made to decrease the dose of hormone required so that if a spontaneous remission is in the offing, it will be discernible through the mist created by administration of the hormone. Lastly, withdrawal should be undertaken only for serious manifestations of Cushing's syndrome or with the prospect of a remission in mind.

This type of therapy requires a close liaison between patient and physician. The patient must know the hazards and should approach the therapy as a calculated risk. His enlightenment is of more importance than the dangers inherent in too much knowledge on his part. There is no doubt in our minds that the intelligent, cooperative patient does better than his opposite.

If the physician is willing to utilize cortisone and corticotropin in this fashion, we feel that their use is worthwhile. We have *nothing* better to offer, and palliation is essentially the function of the physician. Following palliation—relief of pain—functional, social and economic rehabilitation in some degree may be achieved. Even in the most severely damaged patient, a small relief of pain is worthwhile if this does not lead to increased difficulties such as narcotic addiction or to death. By perseverance and diligence on the part of the physician and his careful observation and keen awareness of the problem, palliation may often be achieved without undue hazard to the patient.

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VIRILISM*

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THE sexual deviations found in man occur along iso- or heterosexual lines; in other words, changes are found which are characteristic of the same sex or of the opposite sex. In the isosexual sphere the young female may attain puberty at an earlier age than is normal. In the male, sexual aberrancy may manifest itself in the form of pseudo- or true precocity. In the heterosexual sphere, on the other hand, one finds in the female child or adult, masculinization, while in the male, feminization occurs. The discussion this evening is confined primarily to masculinization, or virilism. Virilism may be defined as the premature or precocious attainment of puberty in the male and masculinization of the female.

Precocious puberty in either sex is due to a premature elaboration of the sex steroids by the gonads or the adrenals. This may occur as a result of some pathological process going on within these glands and it is completely independent of any higher control. On the other hand, and this applies primarily to the gonads, the stimulus may come from the pituitary in the form of a premature secretion of the gonadotropic hormones. The pituitary, in turn, is dependent upon excitation from the higher centers, namely the hypothalamus.

When the underlying aberration arises within the pituitary gland or in the higher nervous centers the same mechanism which normally occurs in puberty ensues. The factors which normally cause the secretion of gonadotropic hormones at puberty do so at a much earlier age. Obviously, such being the case the secretions of the gonads will be normal ones, so leading to a prematurity along isosexual lines. In the female, breast development, ovulation, menstruation and even pregnancy may occur. In the male, there is the early establishment of spermatogenesis in addition to enlargement of the penis and prostate. When

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TABLE I—SEXUAL PRECOCITY OF ISOSEXUAL AND HETEROSEXUAL TYPES

	Male	*Female*
"Hypothalamic"	Brain tumor	Brain tumor
	Encephalitis	Encephalitis
	Congenital defect	Congenital defect
"Pituitary"	Constitutional type	Constitutional type
		Polyostotic fibrous dysplasia with precocity
"Gonadal"	Interstitial cell tumor	Granulosa-cell tumor
	Teratoma	Teratoma
		Chorioepithelioma
		Arrhenoblastoma
"Adrenal"	Congenital hyperplasia	Congenital hyperplasia (pseudohermaphrodite)
	a) pure	a) pure
	b) salt-losing type	b) salt-losing type
	Post-natal hyperplasia	Post-natal hyperplasia
	Tumor (adenoma or carcinoma)	Tumor (adenoma or carcinoma)

Modified after Wilkins, L. "The diagnosis and treatment of endocrine disorders in childhood and adolescence." Springfield, Illinois, C. R. Thomas, 1950.

the site of the pathology is within the target gland itself, either iso- or heterosexual development is encountered.

ETIOLOGY OF SEXUAL ABNORMALITIES

The various glands which are involved in the etiology of sexual abnormalities in man are shown in Table I.

1. *Hypothalamic or Neurological:* The early literature abounds with reports that precocity in the male, and rarely in the female, may be caused by pineal tumors. However, the more recent pathological work of Bing, Globus and Simon[1] and Weinberger and Grant[2] and others, have demonstrated that sexual prematurity occurs with these tumors only when the hypothalamus is invaded. Tumors of the mid-brain, be they primary or metastatic, have also been shown to be accompanied by precocity. In isolated cases it has been found in diffuse inflammatory lesions such as encephalitis, measles, miliary tuberculosis and with certain congenital brain defects. In addition, of course, vegetative disturbances characteristic of hypothalamic disease are present.

Although these diseases occur in equal number in either males or females, the incidence of precocity for some unknown reason is more predominant in the male than in the female (Soffer, Gabrilove, Jailer, and Jacobs[3]).

2. *Pituitary:* Isosexual precocity may occur in a child without any demonstrable pathology. This has been called constitutional precocity and is probably the most common cause of prematurity in the female. This condition is much more common in the female than in the male. There is no evidence of any hypothalamic lesion. These young girls at an early age (as early as two) begin to develop breasts, show some manifestations of sexual hair, and may even ovulate and menstruate. In boys, there is an enlargement of the penis and testis, and the appearance of pubic and axillary hair. Mature sperm and all stages of spermatogenesis are evident. It is well to emphasize at this point that precocity which is under pituitary influence is a complete maturation in all respects in the ovary and the testes.

No pituitary tumor has ever been found to produce precocious puberty in man. This process apparently is a premature physiological awakening of the pituitary-gonadal axis similar to what occurs at puberty. Whatever mechanism is responsible for it then, sets it into motion at an earlier age. These children require no therapy; none is known. Eventually they become normal adults.

McCune and Bruch,[4] Albright,[5] and others have described a rare syndrome which may be of hypothalamic origin in which there is isosexual precocity accompanied by polyostotic fibrous dysplasia. It occurs predominately in the female. There is only one recorded case in a boy and therefore this syndrome does not fall within the scope of a discussion on virilism.

3. *Gonadal:* (a) Ovary. The abnormality responsible for sexual aberrations may rest in a pathological condition of the ovary. This organ may secrete estrogens and thus cause the clinical picture of premature femininity in a young girl. Such has been found to be the case in the rare granulosa cell tumor. On the other hand the pathological condition in the ovary may give rise to the secretion of excessive amounts of androgenic steroids and cause virilism. This may occur either in the child or in the adult woman. It is beyond the scope of this discussion to classify the various pathological conditions known to occur in the ovary. There seems to be some dispute among the patholo-

TABLE II—MANIFESTATIONS OF ADRENAL VIRILISM

Male	*Time of Onset*	*Female*
	CONGENITAL	
Macrogenitosomia praecox		Pseudohermaphrodite
1) Pure		1) Pure
2) With Addisonian-like symptoms		2) With Addisonian-like symptoms
	Hyperplasia > tumor	
	PRE-PUBERALLY	
Macrogenitosomia praecox		Virilism
	Tumor > Hyperplasia	
	POST-PUBERALLY	
(?)		Adrenogenital Syndrome
		Cushing's syndrome—some degree
	Tumor > Hyperplasia	

gists as to the nature of stem cells from which these tumors arise. This has been reviewed and simplified by Teilum[6] and others. A syndrome of polycystic ovaries, amenorrhea, hirsutism and sterility has been described by Stein.[7] However, this may not be true virilism in that the 17-ketosteroid excretion is normal.

(b) Testes. The Leydig cells of the testes are presumably responsible for the elaboration of testosterone. Functional tumors of these cells have been described associated with the manifestations of virilism in young boys. In our series, only one such case has been seen. Oddly enough, in the dog, Sertoli cell tumors have been described which resulted in feminization.

ADRENAL VIRILISM

Clinical Manifestations: A few cases of feminization of males due to adrenal tumors have been described. However, sexual abnormalities of adreno-cortical origin are primarily virilizing.

The clinical manifestations of adrenal virilism are those of excessive androgen secretion. However, the fine details of the syndrome are dependent upon sex and age of the onset of the disease. The various categories found may be classified according to Table II.

Congenital: The disease may have its onset during early fetal life.

This is evidenced by the fact that the external genitalia of the female exhibit alterations characteristic of androgenic stimulation. For example, at birth the infant may demonstrate a large clitoris and there may be only one external orifice which in reality is a urogenital sinus. In many cases, therefore, the sex is either diagnosed incorrectly or is in doubt. These children have the appearance of males with third degree hypospadias and bilateral cryptorchidism. The true sex of these children is often only ascertained after exploration and microscopic examination of a gonadal biopsy. Usually, ovaries are present together with uterus, tubes, and a small vaginal canal which empties into the urogenital sinus. This is the clinical picture at birth of a female pseudohermaphrodite. Since the external genitalia have their embryological origin within the fourth month of development, it is obvious that the disease must have had its origin that early.

The male pseudohermaphrodite is due to an embryological structural defect and apparently has no hormonal basis. In the male the virilizing syndrome may not be as obvious. The children are born with normal genitalia but virilism becomes manifest within the first few years of life, usually by increase in the size of the penis and the appearance of sexual hair.

In both sexes there is a rapid increase in linear growth and these children become very tall for their age. The skeletal x-rays show marked acceleration so that a two or three year old child may show a bone age of that of a ten year old. Hirsutism develops; there is pubic and axillary hair. In the male there is an enlargement of the penis and prostate but not of the testes. These remain consistent with the chronological age. Acne may develop. Voice changes occur. Muscular development becomes obvious.

Due to the advance in the skeletal age the epiphyses close early and it is said that these patients are tall children but short adults.

A rare variant of congenital virilism occurs in which in addition to the usual features there are Addisonian-like symptoms. These patients are usually first seen with extreme dehydration, after having had intractable vomiting. The diagnosis of pyloric stenosis has been made on some. The serum sodium is low and the potassium content of the blood is elevated. These patients exhibit the electrolyte and water difficulties characteristic of Addison's disease. They differ from the true Addisonian in that they have no abnormality in carbohydrate metabolism (Thelan-

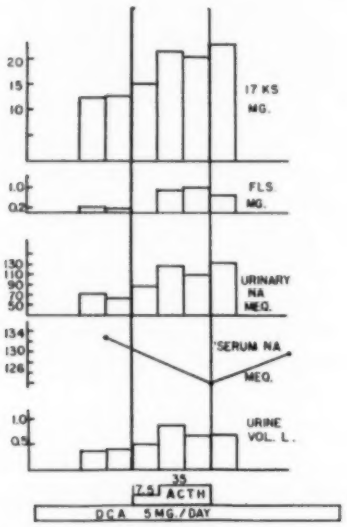

Fig. 1—The effect of ACTH upon Na, 17-ketosteroid and corticoid excretion as well as serum sodium levels in a patient with virilism and Addisonian-like symptoms.

der;[8] Wilkins, Fleischmann and Howard[9]). This condition is more common in male infants than in the female pseudohermaphrodite.

Physiologically speaking it would appear that the pathological adrenals responsible for this syndrome are secreting excessive amounts of androgen, normal quantities of corticosteroids but insufficient salt and water retaining steroids. Recent investigations by Lewis and Wilkins[10] and ourselves[11] have raised the possibility that a desoxycorticosterone antagonist or salt-losing steroid may be elaborated in this condition. The administration of ACTH to such patients results in a loss of urinary sodium and a decrease in serum sodium, although there is ample evidence that adrenal stimulation occurs. The data obtained in such a patient are shown in Figure 1.

The underlying adrenal pathology is invariably bilateral hyperplasia. The adrenal glands, however, may not be grossly enlarged. However, microscopic examination often reveals certain changes especially when the sections are treated with special stains.

Prepuberal: Virilism may have its onset during the postnatal period or early childhood. When this occurs there is no difficulty as to the diagnosis of the true sex of the individual since the normal external genitalia were well developed at birth. In this condition the virilizing syndrome is superimposed upon normal male or female genitalia. The first manifestation of the disease is usually that of accelerated growth. X-ray examination of the skeletal system reveals advance in the bone age. The other signs and symptoms of virilism then develop. In the male the penis is enlarged, the prostate may be palpable while the testes remain small comparable to the chronological age of the child. In the female, this syndrome results in clitoral enlargement. If these manifestations start after the third or fourth year of life, the possibility of an adrenal tumor is great.

Prepuberal adrenal virilism must be differentiated from a normal developmental variant which is called "Precocious adrenarche" (Talbot;[12] Wilkins[13]). In the latter condition there is no great acceleration of growth. The clitoris does not become enlarged and the bone age shows but minor advances in maturation. The clinical picture consists primarily of the early appearance of axillary and pubic hair. These patients must be differentiated from those with true virilism because of the differences in prognosis. Children with precocious adrenarche will eventually develop breasts, ovulate and menstruate and develop into normal adult women.

Postpuberal: Further masculinization of adult man is unknown in clinical medicine; however, adrenal tumors with feminization of the male have been described in the literature. In the female, on the other hand, masculinization may occur. The complete picture of virilism in women consists of hirsutism; amenorrhea; clitoral enlargement; breast atrophy; acne; voice changes; muscular development and loss of libido. This is the syndrome of true virilism and must be differentiated from the common picture of hirsutism which is seen so often. Many of these latter patients menstruate normally and have no difficulty conceiving. As far as we can determine at the present time these women are normal variants.

When a carcinoma of the adrenal is present a mixed syndrome presents itself. Some of the manifestations of Cushing's syndrome may be present along with virilism. There may be hypertension, impaired glucose tolerance, striae and sometimes osteoporosis.

TABLE III—17-KETOSTEROID VALUES IN PATIENTS WITH "ADRENAL VIRILISM"

Patient	*Age*	*Sex*	*17-ks (mg. per day)*	*Remarks*
			Adrenal Hyperplasia	
A. R.	8 months	F	11.3	Pseudohermaphrodite
T. K.	4 years	F	26.0	Pseudohermaphrodite
	14 years		34.2	
C. R.	7 years	F	42.8	Pseudohermaphrodite
	12 years		62.4	
B. L.	15 months	F	9.0	Pseudohermaphrodite
C. D.	2½ years	F	16.5	Pseudohermaphrodite
J. L.	13 years	F	46.1	Pseudohermaphrodite
K. A.	14 years	F	46.7	Pseudohermaphrodite
R. E.	10 years	F	17.2	
R. K.	8 years	F	19.8	
B. F.	4½ years	"F"	9.8	True hermaphrodite with virilism
E. B.	5 years	M	24.8	Macrogenitosoma praecox
	7 years		28.2	
J. T. T.	6 years	M	17.4	Macrogenitosoma praecox
W. H.	3¾ years	M	21.6	Macrogenitosoma praecox
A. R.	9 years	M	19.2	Macrogenitosoma praecox
S. B.	2½ years	F	5.5	Pseudohermaphrodite with addisonian-like symptoms
L. Y.	15 months	M	11.1	Virilism with addisonian-like symptoms
			Adrenal Adenoma	
F. N.	7 years	M	175	Adrenal adenoma
			6	After removal
M. H.	6½ years	F	189	Adrenal adenoma
			4	After removal
			Adrenal Carcinoma	
K. C.	42 years	F	37.8	Mixed syndrome—Cushing and virilism

The disease in this age group is more likely to be due to an adrenal tumor than bilateral adrenal hyperplasia. True virilism must also be differentiated from the so-called Stein-Leventhal syndrome of polycystic ovaries, amenorrhea and hirsutism.

Steroidal Findings: It is in the virilizing syndrome that the determination of the urinary 17-ketosteroids is of greatest diagnostic value. It must be borne in mind that the urinary 17-ketosteroids are composed

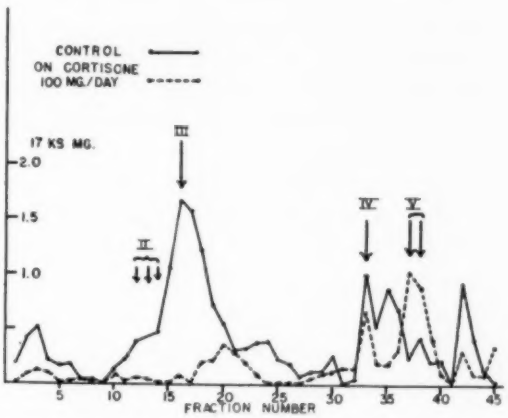

Fig. 2—Chromatographic pattern of 17-ketosteroids in adrenogenital syndrome.

Control	*On Cortisone*
II—dehydroisoandrosterone	IV—etiocholanolone
III—androsterone	V—11-keto-etiocholanolone

of several different steroids which are of testicular and adrenal origin in the male while in the female, presumably, only of adrenal origin. The four 17-ketosteroids found in the urine in the highest concentration are androsterone, etiocholanolone, dehydroisoandrosterone and 11-keto-etiocholanolone. The latter steroid together with 11-hydroxy-androsterone are probably degradation products of cortisone or Compound F and are therefore of adrenal origin. The origin of the first three on the other hand is not as definite. Androsterone and etiocholanolone are found in the urine of patients who receive testosterone and therefore are presumably of testicular origin. But what the adrenal precursors of these substances are in the female has not been definitely established.

The urinary 17-ketosteroids are present at birth in trace amounts and from birth to about ten years of age there is a gradual increase in the values rising from about 0.5 to 4 mg. From this age to puberty, there is a more accelerated rise to adult levels. This increase occurs in both boys and girls. In our laboratory, young adult males excrete between 10 and 20 mg. per day while females excrete between 6 and 15 mg. per day.

The 17-ketosteroids are invariably elevated in adrenal virilism but they may not be markedly so (Table III). The separation and identification of the various steroids by means of chromatography has been accomplished in our laboratory. The same steroids which are present in normal adults are found but in higher concentration in patients with adrenal hyperplasia (Figure 2).

Increased amounts of dehydroisoandrosterone, a β-ketosteroid, has been found in the urine of patients with a virilizing adrenal tumor by Talbot et al.;[14] Mason;[15] Allen et al.[16] Allen has proposed a simple color test for this steroid. However, this reaction does not appear to be specific enough. Our own experience with adrenal tumors has demonstrated the great variation in the concentration of the dehydroisoandrosterone in patients with adrenal tumors. We have analyzed the urine of two patients with adrenal carcinoma in whose urine no increase in this steroid was found.

Other steroids have been found in high concentration in adrenal virilism. Pregnanediol and pregnanetriol have been found by Butler and Marrian[17] and others. Large amounts of estrogens, paradoxically enough, have been found in the urine of such patients, although these patients show no manifestations of estrogen secretion (Jailer;[18] Wilkins[19]).

Differential Diagnosis: The finding of precocious sexual development along isosexual lines in the female tends to rule out the adrenal as the source of the pathology. Precocious puberty in the female is due to pituitary stimulation or an ovarian tumor. In the young girl true virilism must be differentiated from that syndrome of precocious adrenarche. In the latter condition 17-ketosteroids are but slightly elevated. The bone age may not be advanced. Children usually do not show the marked acceleration of growth nor is there any evidence of clitoral enlargement. As an illustration, we recently have seen an eight and one-half year old girl who within the past year had developed axillary and pubic hair. This child had never shown an acceleration in growth; her bone age was normal, the clitoris was not enlarged. The values of 17-ketosteroids which were determined in another laboratory were above 20 mg. per day. A peri-renal air insufflation was performed to detect the presence of an adrenal tumor. It was normal. This clinical syndrome is not consistent with adrenal virilism. When the 17-ketosteroid determination was repeated in our laboratory, normal values were obtained.

TABLE IV—ADRENAL HYPERPLASIA
THE EFFECT OF CORTISONE ON 17 K-S EXCRETION

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Control	17.2	37.1	68.0	25.5	60.6	20.0	8.9	9.6
	18.2	34.2		31.0	57.7	21.6	14.1	
	26.5	30.1	69.5	29.9	58.9	17.6	16.5	11.6
	13.4				54.0			2.7
	11.7			16.1	42.7			3.5
Cortisone	4.8	11.2	33.2	13.0	37.5	2.4	4.7	5.0
	3.8	15.1	16.5	15.0	12.9			
	5.4		14.4	9.7	7.7			
			9.9					
Dose	100 mg.	200 mg.	200 mg. "F"	200 mg.	100 mg. "F"	100 mg.	50 mg.	100 mg.

In the male, enlargement of the testes and premature maturation of the spermatogenic elements occur when the precocious puberty is due to testicular stimulation by the pituitary. In adrenal virilism, this does not occur. The clinical pictures aside from this finding are identical. In constitutional precocious puberty the 17-ketosteroids are not markedly elevated.

Differentiation of Adrenal Tumor from Adrenal Hyperplasia: The presence of an adrenal tumor may occasionally be demonstrated roentgenologically by displacement of the kidney. This may be seen on a simple flat plate of the abdomen or it may be necessary to do an intravenous pyelogram. Peri-renal air insufflation is also a valuable tool. However, as is well known, even these diagnostic procedures may fail to detect the presence of a tumor.

Response to Cortisone: Cortisone and Compound F (which appears to be the steroid secreted by the adrenal) have definite physiological effects which are well known. One of these effects is the inhibition of ACTH secretion by the pituitary. If given over a long period of time cortisone may even cause adrenal atrophy (literature reviewed by Ingle[20]). It has been shown by Wilkins[19, 21] and his collaborators, Bartter and Albright[22] and by Jailer, Louchart and Cahill[11, 23] that the administration

TABLE V—ADRENAL NEOPLASM
THE EFFECT OF CORTISONE ON 17 K-S EXCRETION

	* 1	* 2	† 3	* 4
Control	37.7	26.0		51.6
	35.8			40.8
	37.2	20.1	14.9	39.3
	33.8	21.3		53.1
	40.5	17.7		56.1
Cortisone	43.8	20.7		63.0
	36.0	18.5	14.3	
Dose	200 mg.	200 mg.	100 mg.	100 mg.

* Adrenal carcinoma
† Adrenal adenoma

of adequate amounts of cortisone to patients with virilism accompanied by adrenal hyperplasia results in a fall of the 17-ketosteroids from their characteristic high levels to values approximately normal for the age and sex of the patient. Table IV shows such ketosteroid decreases in eight patients with documented adrenal hyperplasia. The steroidal levels remain low as long as cortisone is administered. In our clinic we have under treatment at the present time eighteen such patients.

Figure 2 shows two ketosteroid patterns of the same patient before and during cortisone therapy. The peaks that disappear have been identified as androsterone and etiocholanolone. The steroid that increases in concentration is 11-keto-etiocholanolone which is a known degradation product of cortisone.

However, if an adrenal tumor is present the response to cortisone is quite different. Table V illustrates the data obtained in four patients with adrenal tumors. Patients 1 and 2 had adrenal carcinoma with the virilizing syndrome. It is obvious from the data that the administration of cortisone to these two patients had no effect on the urinary 17-ketosteroids. Patient No. 3 had an adrenal adenoma and in this condition as well, no fall in 17-ketosteroids occurred as a result of cortisone administration. Patient No. 4 suffered from Cushing's syndrome which was caused by an adrenal carcinoma and it is of interest that in this condition as well the injection of cortisone had no effect upon the urinary

excretion of 17-ketosteroids.

It should be emphasized, however, that the fall in the urinary 17-ketosteroids as a result of cortisone administration is not characteristic of only adrenal hyperplasia. Similar but not as marked a decline in steroid excretion occurs in normal individuals, in patients with precocious adrenarche and also with Cushing's syndrome when they are given cortisone. It can not be used as a diagnostic test for adrenal virilism. Its only value lies in differentiating the tumor from hyperplasia within the adrenogenital syndrome.

Since one of the effects of cortisone is to inhibit pituitary ACTH secretion, the above results may indicate that the hyperplastic adrenal glands remain under pituitary control whilst the tumor (adenoma or carcinoma) is independent of pituitary domination.

Treatment: The treatment of adrenal virilism with cortisone has been anticipated in the previous section. The rationale of such treatment is to remove the tropic hormone and place the pathological adrenal in a state of rest while at the same time supplying a more normal adrenal steroid, namely cortisone or Compound F. It is well to emphasize that the dosages used need not be as high as those used in the treatment of rheumatoid arthritis or other collagen diseases. In the latter diseases one must achieve the "hyperadrenal state" in order to obtain a remission. This is apparently a pharmacological effect; on the other hand, in adrenal virilism the object is a more physiological one, namely the inhibition of pituitary ACTH secretion. Therefore, smaller doses of cortisone suffice.

In our experience the dosage varies from individual to individual but if the urinary 17-ketosteroids excretion values are followed the dosage can be adjusted easily for each individual. An attempt is made to keep the 17-ketosteroids as close to normal as possible; often 100 mg. of cortisone given intramuscularly three times a week or 25 mg. a day will be sufficient to achieve this end. Apparently cortisone by mouth is not as effective as when administered by the intramuscular route. The reason for this is unknown. It may take two or even three times the dosage of cortisone to achieve the same fall in the urinary 17-ketosteroids when the steroid is given orally as contrasted to the intramuscular route.

The salt-losing type of virilism as mentioned earlier in this discussion can be controlled as well as the pure virilizing syndrome. One of our

patients with this condition who, previous to the advent of cortisone, was admitted to the hospital on several occasions in Addisonian crises because of upper respiratory infections, although he was maintained on 5 mg. a day of desoxycorticosterone acetate and 5 gm. of added salt, has remained perfectly healthy since he has been on the cortisone regimen together with added salt. In fact, he has been admitted but once—to have his tonsils removed and underwent that operative procedure uneventfully.

In younger children there has been a slowing down of the accelerated growth, so characteristic of this disease. We have seen severe acne disappear; and in one patient (the only one in our series with hypertension) there was a fall in the blood pressure on cortisone therapy. Wilkins[24] has had similar results in three patients exhibiting hypertension. In our series we have five girls between the ages of fourteen and seventeen on cortisone therapy; three are now menstruating regularly while receiving cortisone. No estrogen or progesterone has been added to the regimen. In these girls there have been increased breast development and the achievement of a more feminine habitus.

It is of interest to speculate as to the mechanism of the dramatic results achieved with cortisone therapy. The secretion of the gonadotropic hormones can be inhibited by large doses of androgens and gonadotropic titers are low in these patients. Since cortisone causes a marked fall in androgen secretion by the adrenals, it indirectly frees the pituitary gonadotropins from the androgen inhibition. Thus, it follows that the pituitary will now secrete its FSH and ICSH which in turn stimulate the ovary. This is schematized in Figure 3.

When an adrenal tumor is present the treatment of choice is surgery and if the tumor is completely removed there is a marked fall in the urinary 17-ketosteroids and a cessation of the progress of the disease. In the past it has always been hoped that a tumor was present because only under these conditions could definitive therapy be achieved.

The Metabolic Defect in Adrenal Virilism

Adrenal virilism is often a congenital disease. It may occur in several siblings within a family. Consequently congenital adrenal hyperplasia may be due to some inborn error of metabolism. We have been extremely interested in this phase of the problem and have conducted studies attempting to elucidate the underlying metabolic error in these

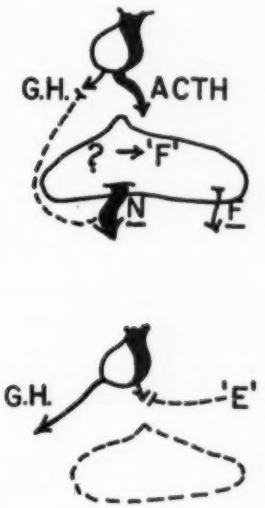

Fig. 3—Schematic representation of the action of cortisone in adrenal virilism. "G.H."—gonadotropic hormone
"F" —Compound F
"E" —Cortisone
"N" —"N" hormone or androgen

TABLE VI—THE EFFECT OF 17-OH-PROGESTERONE ON 17-KETOSTEROID EXCRETION

FEMALE PSEUDOHERMAPHRODITE

Day	*17 KS mg./day*	*Treatment*	
1	8.0	None	
2	9.1	None	
3	6.8	150 mg. Cortisone	
4	3.8	150 mg. Cortisone	
5	4.2	150 mg. Cortisone	
6	11.8	150 mg. Cortisone	300 mg. 17OH Prog.
7	19.2	150 mg. Cortisone	300 mg. 17OH Prog.
8	24.5	150 mg. Cortisone	300 mg. 17OH Prog.
9	21.4	150 mg. Cortisone	

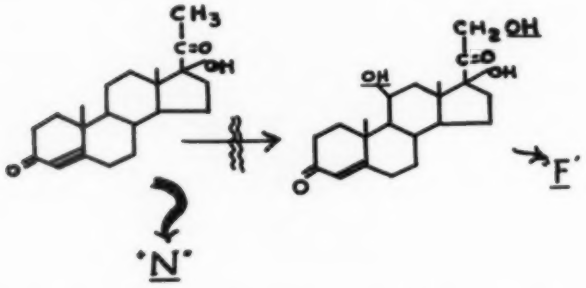

Fig. 4—Schematic representation of metabolic defect within adrenal gland in virilism.

pathological adrenals. From our studies the following points have emerged:

1. The administration of ACTH has demonstrated a distinct difference in response between patients with adrenal virilism as contrasted with normals. Apparently these patients have difficulty synthesizing the normal adrenal steroid, Compound F. ACTH results in no increase in oxysteroid secretion; no consistent fall in the eosinophiles; and no sodium retention. However, there is an increase in 17-ketosteroid and pregnanediol excretion. These adrenals show little evidence of corticoid secretion but elaborate 17-ketosteroid precursors.

2. It has been shown by Hechter, et al.,[25] and Hayano and Dorfman[26] and others that adrenal tissue is capable of hydroxylating 17-hydroxyprogesterone to Compound F.

3. 17-hydroxyprogesterone is *androgenic* (Pfiffner and North[27]) and not progestational. When given orally to man it causes an increase in 17-ketosteroid excretion (Table VI).

4. It is possible that the enzyme system which is normally responsible for the hydroxylation at the C-11 and C-21 position in the synthesis of Compound F may be deficient. Thus the synthesis of Compound F would stop at the 17-hydroxyprogesterone stage (Figure 4). Consequently, this normal intermediary in the synthesis of Compound F may be the steroid which is secreted by these adrenals, and is converted by the liver to an androgen. Since insufficient quantities of "F" would be secreted, the pituitary would now secrete excessive amounts of ACTH, cause an hypertrophy of the gland, which would now secrete a normal

amount of Compound F for homeostasis. In order to achieve this, excessive amounts of 17-hydroxyprogesterone would be elaborated. This may be the androgen responsible for the virilism. We have obtained further circumstantial evidence for this hypothesis which is beyond the scope of this discussion.

If this be correct, congenital adrenal virilism must be considered an inborn error of metabolism in which one of the normal intermediaries in the synthesis of Compound F piles up in the gland and is secreted. It so happens that this intermediary is androgenic after it has been metabolized by the liver.

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AN EVALUATION OF THE USE OF RADIATION IN THE TREATMENT OF ENDOMETRIAL CANCER*

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Seventh James Ewing Memorial Lecture

THE opportunity to present the Ewing Memorial Lecture is an occasion for which I am most grateful. It is an honor to address you under those auspices. My appreciation comes also from the fact that Dr. Ewing was one of my teachers. Upon receiving the invitation some months ago, I could not escape the hope that the work to be presented might be of a quality commensurate with the memory of the distinguished gentleman we are honoring. The high esteem in which he is held, however, makes that task extremely difficult. It must be admitted that those first ambitions have not been fulfilled, but perhaps these remarks will serve as an expression of personal appreciation, and as another acknowledgement of his profound influence upon medicine.

James Ewing had more than anatomical interest in cancer. At times he seemed fascinated by the response certain tissues showed to irradiation. His interest in the genesis and clinical behavior of tumors is evident throughout his principal arbeit, "Neoplastic Diseases." In pursuing the study of neoplasms he must have given considerable thought to the physiology and behavior of certain genital epithelia, such as the cyclical alterations occurring in endometrium. The periodic shedding, repair, and reconstruction, as well as the remarkable potential for hypertrophy during gestation, present a striking example of orderly and controlled growth. The close histologic similarity between certain hyperplasias and the more differentiated malignant neoplasms have been of speculative interest in the histogenesis of endometrial cancer. The tendency for

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endometriosis to spread, in spite of benignity, parallels the extension of cancer by direct growth and dispersion. It is deemed appropriate, therefore, to select endometrial cancer for discussion here, and in particular the use of preoperative irradiation, which, after a considerable number of years, still presents a rather confused and fluid problem.

The incidence of endometrial cancer reported in most cancer clinics is low in comparison with that for cervical lesions. Some general hospitals, on the other hand, report a more equal distribution. The higher ratio in general hospitals indicates initial clinical symptoms are often attributed to benign causes. Furthermore, the generally accepted concept of endometrial cancer may mitigate against establishing diagnosis before operation, as well as recognizing need to segregate suspected cases into groups for special procedures. With indication for operation, which may be nothing more than excessive bleeding, surgery is performed without loss in time or economy incurred by curettement. If at operation endometrial cancer is found, simple total hysterectomy is considered adequate treatment in the belief that the tumors are slow to spread, and remain for a long while within limits of the myometrium. Risk of dispersion of contamination at operation is believed controlled by closing points of tumor escape through the cervical canal, or through fimbriated ends of fallopian tubes.

The fact that a large percentage of patients present operable lesions favors the generally accepted concept for endometrial cancer. Furthermore, collected statistics for simple total hysterectomy show a five-year survival rate on the order of 65 per cent. The concept fails to take into account, however, any data obtained by preoperative diagnosis that might indicate patients treated inadequately by that procedure. Improvement in clinical results is to be expected if methods of treatment are modified to meet more adequately any individual variations in range and promptness of spread, or in susceptibility to irradiation. Data of that order might best be obtained by exploration of the uterus and removal of tissue for histologic examination. It is to be admitted that preliminary curettage increases cost of patient care and delays definitive treatment. It has also been contended that such a procedure incurs risk of dispersion. It is our opinion, however, that data obtained by curettement are of value that offset any disadvantages. High incidence of correct diagnosis following use of the Randall curette has been reported by Wall.[1] Employed as an office or clinic procedure the problem

in economy and in loss of time is lessened. Positive diagnosis eliminates need for curettement, but that procedure is not omitted if only benign tissue is obtained.

Due to the fact that endometrial lesions are predominantly glandular in type, and present varying degrees of secretory activity, the use of radiation in operable patients may not be considered necessary or practical. Patients treated by irradiation alone are usually those found to be inoperable by extension of tumor, or those with some associated constitutional condition increasing risk of surgery. The frequent association of endometrial cancer with obesity, hypertension, diabetes, advanced age, et cetera, is well known. Those patients present a poorer prognosis, and the lesser results obtained in that group have very likely contributed to the belief that endometrial cancer is not well suited to irradiation. Heyman,[2] on the other hand, obtained among operable patients a five-year survival rate in excess of 60 per cent for treatment by radiation alone. That value resulted directly from advance in technique of radium treatment. Inadequacies of the usual intra-uterine tandem were lessened by packing the uterine cavity with radium tubes introduced individually until all the available space became filled. Other authors have attempted to improve the distribution of radiation by devising hysterostats of different types. Among the older applicators are those devised by Dietel,[3] and the "Y" shaped applicator still in use at the Schmitz clinic in Chicago.[4] Crossen,[5] Friedman,[6] and several others have described special devices.

It is not our intention here to become involved in a comparison of the relative merits of radiation versus surgery in the treatment of endometrial cancer. That question could become more complex than it is today in the management of cervical cancer. In point of fact it is almost impossible to attempt such a comparison for endometrial cancer, due to irregularities in type of clinical material. Several authors have proposed classifications specifying differences in size and extent of tumor. Those depend largely upon examination of the removed uterus, however, and are of little value in clinical examination because pathways of spread for endometrial cancer are not accessible to palpation. Heyman[2] proposed a classification of considerable merit. Patients suited to hysterectomy are termed "clinically operable." Those presenting operable lesions not suited to surgery due to some associated constitutional disorder are grouped "technically operable." The term "inoperable" is applied to

lesions with extension making hysterectomy impractical. Patients presenting downgrowth into the cervix are kept statistically separate in a group called "corpus et collum."

The Editorial Committee charged with issuing the annual reports for the League of Nations study of cervical cancer, adopted in 1950 a stage-grouping for use in reporting results obtained in treatment of endometrial cancer. Emphasis is given the importance of staging based upon clinical examination prior to treatment, and not influenced by any findings at operation. The essential data are:

Stage O: Histological findings considered likely to be cancer, but inadequate for definite microscopic diagnosis.

Stage I: Tumor is confined to uterus
(a) Operation advisable
(b) Bad operative risks

Stage II: Tumor has spread outside the uterus.

The need for a uniform clinical classification to be used in comparing end results in cancer was emphasized many years ago by Bilroth. Stage-grouping is as essential in endometrial cancer as it is in cervical cancer. A substantial percentage of patients fall into Stage Ia. Attempts to improve clinical results by more radical surgery are handicapped by obesity, and the considerable incidence of associated conditions that increase risk of more extensive surgery. In this country, but not so much abroad, the attempt has been made to improve results by combining radiation with surgery. Stimulus for that scheme has come chiefly from the early work of Henry Schmitz,[4] William Healy,[7] and their co-workers, in which Dr. Ewing had more than an indirect part. Others pursuing the problem include Scheffey,[8] Payne,[9] Herbert Schmitz,[10] Corscaden,[11] Miller,[12] Taylor,[13] and McKelvey.[14] In general, the use of preoperative irradiation has been preferred because a greater tumor dose is attained by combining intra-uterine radium with external irradiation.

Despite the fact that use of radiation with surgery has not been particularly satisfactory in cervical cancer, the combined treatment in endometrial cancer is aimed at meeting more effectively the natural history of that disease. Nevertheless, the mechanism by which preoperative irradiation may improve clinical results remains vague. The importance of degree of differentiation and of uterine size in prognosis has been debated for different methods of treatment without definite conclusion. In a recent report by Herbert Schmitz[10] no close relation was noted

between degree of differentiation and prognosis, or with size of uterus. He did, however, find stage of clinical advance a more significant factor in clinical results. His data are among the few that attempt to compare results upon the basis of stage of advance. A point in general agreement is that disappearance, or control of tumor within the uterus, as determined microscopically in the specimen removed after preoperative irradiation is associated with an extremely favorable outlook. Schmitz obtained that result in about three-fourths of his patients, and has for that group a five-year survival in excess of 85 per cent. Similar results have been reported by Taylor and Becker.[13]

McKelvey[14] has lately questioned the usefulness of radiation in the combined treatment. After eliminating the use of x-rays at one period, and of radium at another, he has experienced with increased operability a steady advance in average results for his total series of patients. It is contended that the application of surgery to a greater percentage of patients is responsible for the advance. What part improvement in type of clinical material may have exercised is uncertain. Very properly, however, he criticizes the selectivity that must be exercised in assigning patients for a particular treatment, and attempting to evaluate results upon that basis. In the absence of a generally accepted classification of clinical stage, considerable confusion is to be expected. Furthermore, if a suitable stage-grouping were in general use it is not likely that definite conclusions upon treatment would be established. The respective roles of surgery and radiation are not clearly defined in the treatment of cervical cancer.

Henriksen,[15] Javert,[16] and others have demonstrated for endometrial cancer a tendency toward spread that is greater than generally believed. Lymph node dispersion is important. In addition to the main lymphatic pathways passing lateralward to the regional nodes in the iliac region, it is probable that endometrial cancer may undergo dispersion through ovarian lymphatics connecting with nodes higher in the lumbar chain, as well as through the intimate anastomoses between lymphatics of the uterus and the vagina. Those pathways of spread must be responsible for many therapeutic failures. Control of lymph node metastases by irradiation is highly disputed in cervical cancer. It is not likely that evidence will be forthcoming to show more clearly any effect in endometrial cancer. At the same time improvement in clinical results following preoperative irradiation implies extension of

effective treatment beyond that attained by hysterectomy. Explanation of that question makes important the accumulation of data upon factors responsible for tumor disappearance within the uterus, which, at present, is the most significant prognostic sign in endometrial cancer. It is presumed that preoperative irradiation devitalizes tumor to a degree that lessens risk of spread or contamination at operation. There is general agreement that vaginal irradiation lessens the incidence of vaginal recurrences and metastases. The effects of size of uterus and of degree of differentiation upon prognosis have been difficult to evaluate.

About 1938 we began use of preoperative irradiation at Barnes Hospital, and at the Barnard Free Skin and Cancer Hospital. A course of external roentgen irradiation has initiated the treatment in most instances. In the attempt to avoid intestinal sequelae the amount of irradiation applied to clinically operable patients has been only about two-thirds that generally employed in cervical cancers. Modifications in technique and in dose have been made from time to time in the attempt to increase effectiveness of x-rays, but most of the patients now available for five-year statistics received approximately 1500 r (air) to each of four fields measuring 10 cm. by 15 cm. Patients selected for irradiation alone received about 2400 r (air). Radium is applied near the end of roentgen treatment using one application in clinically operable cases, and two or more in those not to be operated upon. In collaboration with Nolan[17] a method was devised for introducing radium capsules into the uterine cavity that simulates the packing technique described by Heyman.[2] In the earlier years there was considerable variation in length and strength of radium sources, but greater standardization has been attained since 1946.[18] Intravaginal radium was held in place by means of sponge rubber applicators, but more recently we have used modification of the Manchester ovoids, as well as special applicators, devised by Fletcher.[19]

With the aim of evaluating preoperative irradiation we have reviewed the primary cases given definitive treatment during the years 1930-1947 at the Barnard Free Skin and Cancer Hospital and upon the clinic service at the Barnes Hospital. Patients first treated elsewhere, or those given only palliative irradiation, and all private cases have been deleted. Survival rates to be given are relative values. All patients with endometrial cancer are to be included in a more detailed report to be made later by Dr. Sherman.

TABLE I—FIVE-YEAR RESULTS IN 197 PRIMARY CASES OF ENDOMETRIAL CANCER TREATED AT THE BARNARD FREE SKIN AND CANCER HOSPITAL AND UPON THE WARD SERVICE OF THE BARNES HOSPITAL 1930-1947

Treatment	*Classification*	*Five Year Result (Relative)*		
		Number of Patients	*Alive and Well*	*Per Cent*
Irradiation	Technically Operable and Inoperable	94	23	24.5
Irradiation and Hysterectomy	Clinically Operable	60	42	70
Hysterectomy	Clinically Operable	43	29	67.7
Total		197	94	47.7

Operability—52.3 Per cent. Lost to Follow-Up—10 Per cent.

In Table I, it can be seen that a total of 197 patients are included. Of that number ninety-four were considered inoperable for one reason or another. Hysterectomy, with or without preoperative irradiation, was performed in the remaining 103, presenting an operability rate of 52.3 per cent. For the entire series there is five-year survival free of recurrence of 47.7 per cent. In the group with poor prognosis treated by irradiation alone the value is only 24.5 per cent. For the sixty patients given preoperative irradiation there is a survival rate of 70 per cent, and for hysterectomy alone a value of 67.7 per cent. The difference in results with and without preoperative irradiation in clinically operable patients is of doubtful statistical significance. While the survival rate given for hysterectomy alone is in agreement with that established for that method in collected statistics, any superiority for the combined treatment is not demonstrated in this comparison. Analysis of clinical material might reveal a better prognosis for one group or the other, but those data are not apparent in a table showing total results.

It can be demonstrated that the technique of radium treatment has a determining effect upon results following irradiation. In Table II it can be seen, that, among the ninety-four patients treated by irradiation alone, only 12.5 per cent survived if radium was applied as an intrauterine tandem, but 30.6 per cent of those given multiple capsules are alive and well at the end of five years. Extending that comparison to the sixty patients given combined treatment, it can be seen that the value for

TABLE II—FIVE-YEAR RESULTS FOLLOWING USE OF INTRA-UTERINE TANDEM AND OF MULTIPLE CAPSULES CONTAINING RADIUM IN PATIENTS RECEIVING RADIATION ALONE OR IN CONJUNCTION WITH HYSTERECTOMY

Treatment	*Radium*	*Five Year Result*		
		Number of Patients	*Alive and Well*	*Per Cent*
Irradiation Only	Tandem	32	4	12.5
	Multiple Capsules	62	19	30.6
Irradiation and Hysterectomy	Tandem	15	8	53
	Multiple Capsules	45	34	75.5

intra-uterine radium tandem is 53 per cent, and that for multiple capsules is 75.5 per cent. Explanation of a survival rate for tandem and hysterectomy falling below that expected for surgery alone cannot be made except upon the basis of other factors in prognosis. For multiple capsules, on the other hand, the value of 75 per cent is a ten point improvement above the average for surgery alone, and represents an advance of 10/65, or about 15 per cent. Mention should be made of the small number of patients in each group. Caution must be used in making conclusions. In the attempt to evaluate results in such a series, considerable fluctuation in results is to be expected.

Measurement of 12.0 cm. or more in depth of uterine cavity has been taken arbitrarily as evidence of enlargement. Analysis of results according to uterine size is given in Table III. Evidence of extension outside the uterus was noted at operation in only four patients, three of whom received preoperative irradiation. Due to the small number of patients with extension, no attempt has been made to consider the added effect of uterine size in that group. The marked effect of extension on prognosis is demonstrated by the fact that only one of the patients survived the five-year period.

Among patients without demonstrable extension, depth of uterine cavity was less than 12.0 cm. in sixty-five. Preoperative irradiation was employed in thirty-two of that number, of whom twenty-eight or 87 per cent survived. The value of hysterectomy alone is 26/33, or 79 per cent. Larger uteri were found in thirty-four patients. Results after preoperative irradiation are 13/25, or 52 per cent, and for hysterectomy alone 3/9, or 33 per cent. Those data are in agreement with earlier

TABLE III—FIVE-YEAR RESULTS IN 103 CLINICALLY OPERABLE PATIENTS GIVEN PREOPERATIVE IRRADIATION OR TREATED BY HYSTERECTOMY ALONE

The patients have been divided into groups according to uterine size and extension of tumor outside the uterus.

Depth of Uterine Cavity cm.		*Pre-Operative Irradiation*			*Hysterectomy Only*		
		Number of Patients	*Alive And Well*	*Per Cent*	*Number of Patients*	*Alive And Well*	*Per Cent*
Less Than 12 cm. No Extension	Tandem	8	7	87			
	Multiple Capsules	24	21	87			
	Total	32	28	87	33	26	79
More Than 12 cm. No Extension	Tandem	6	1	17			
	Multiple Capsules	19	12	63			
	Total	25	13	52	9	3	33
Any Depth With Extension	Tandem	1	0	0			
	Multiple Capsules	2	1	50			
	Total	3	1	33	1	0	0
		60	42	70	43	29	67.7

observations that uterine enlargement affects prognosis adversely. Use of preoperative irradiation resulted in survival better than that following hysterectomy alone. The degree of improvement is found to be greater in patients with enlarged uteri. In that group the technique of radium treatment is important, and improvement in results occurred only in those treated by insertion of multiple capsules. Mention should be made of one other point shown in Table III. It can be seen, that, among the forty-three patients treated by surgery alone, there are thirty-three with uteri less than 12.0 cm. cavity depth. Upon that basis prognosis is expected to be better than for the patients given preoperative irradiation. That factor is of significance in considering the slight degree of improvement in results shown for combined treatment in Table I.

Relation of histology to end results is shown in Table IV. Division is made into differentiated and undifferentiated forms. Incidence of

TABLE IV—FIVE-YEAR RESULTS IN 103 CLINICALLY OPERABLE PATIENTS THE TUMORS ARE DIVIDED INTO DIFFERENTIATED AND UNDIFFERENTIATED FORMS

	Pre-Operative Irradiation			*Hysterectomy Only*		
Histological Type	*Number of Patients*	*Alive And Well*	*Per Cent*	*Number of Patients*	*Alive And Well*	*Per Cent*
Differentiated	38	29	76	27	24	88
Undifferentiated	22	13	59	16	5	31
Total	60	42	70	43	29	67.7

those types is almost identical in the two methods of treatment. Among differentiated tumors the combined method of treatment resulted in survival of twenty-nine of the thirty-eight patients, or 76 per cent. The value for hysterectomy alone is 24/27, or 88 per cent. Preoperative radiation is not expected to lessen survival rates, but is here not shown to improve clinical results. The better value for surgery alone may be due to other factors affecting prognosis, such as uterine size. Among undifferentiated tumors, however, improvement following preoperative irradiation appears significant. As can be seen in the table, five-year survival is found for thirteen of twenty-two patients, or 59 per cent, but for only five of sixteen patients, or 31 per cent of those treated by hysterectomy alone.

Disappearance of tumor within the uterus following preoperative irradiation has been stated to be one of the more significant signs of favorable prognosis. Factors affecting tumor control are, therefore, of importance in the attempt to improve clinical results. In this series the status of tumor after irradiation has been determined by examination of routine sections made in the diagnostic laboratories. No special search has been conducted by increasing the number of blocks of tissue taken from each specimen beyond the needs dictated by adequate microscopic diagnosis. Data upon the sixty patients given the combined treatment are shown in Table V. Tumor control is reported in sixty-six per cent. Histological characteristics have relationship to regression. Control is found in 70 per cent of differentiated lesions, but in only 60 per cent of undifferentiated forms. There are, however, other factors that affect tumor response, such as technique of radium treatment. Those data are not given in the table. Disappearance of tumor has been noted in

TABLE V—FIVE-YEAR RESULTS IN 60 CLINICALLY OPERABLE PATIENTS GIVEN THE COMBINED TREATMENT

The patients have been divided into those showing evidence of tumor control within the uterus, and those showing persistent cancer. Results are shown for differentiated and undifferentiated forms.

		Controlled			*Uncontrolled*		
Histological Type	*Number Treated*	*Number of Patients*	*Alive And Well*	*Per Cent*	*Number of Patients*	*Alive And Well*	*Per Cent*
Differentiated	38	27	24	88.8	11	5	45.5
Undifferentiated	22	13	11	84.6	9	2	22
Total	60	40	35	87	20	7	35

	Total Series	Differentiated	Undifferentiated
Tumor Control Obtained:	40/60—66 Per Cent	27/38—70 Per Cent	13/22—60 Per Cent

three-fourths of patients treated by insertion of multiple capsules, but that effect is noted in less than half the patients treated by intra-uterine tandem. The importance of tumor control is significant. Among the forty patients showing that phenomenon, there is survival of thirty-five, or 87 per cent. Persistent tumor is noted in twenty patients, of whom only seven, or 35 per cent are alive and well. Those results are in close agreement with experience reported by other authors.

Table V includes other data of considerable interest. Among patients with tumor control the survival of differentiated and undifferentiated forms is uniformly good. The respective values are 88.8 per cent, and 84.6 per cent. Similar conditions do not prevail for those with persistent tumor in the uterus. Despite the fact that the number of patients showing residual cancer is so small that results cannot be of more than speculative interest, it should be noted, that, in addition to the overall survival being materially less, a distinct difference is noted for the two histologic groups. Five-year survival in the undifferentiated cases is only half that for the differentiated ones. It should further be noted that tumor control is more difficult to attain for undifferentiated cancers, and occurred in only 60 per cent. Among those treated by insertion of multiple capsules the incidence is somewhat higher. If we consider the 85 per cent survival for those showing tumor control, and add to that number the 20 per cent salvage of those without control, we find the 59 per cent result shown for the combined treatment in Table IV. In a broad sense that indicates a favorable result in about two of three patients for preoperative irradiation, but only in one of three individuals with undifferentiated cancer treated by hysterectomy alone.

Analysis of results in our series of patients does not specifically clarify the confused and fluid problem mentioned in introducing the question of preoperative irradiation for this discussion. The relatively small number of patients falling into the various subdivisions created for study limits conclusions that can be made in a broad statistical sense. In spite of that, however, the experience gained here, combined with that reported by other authors, presents factual data that establish usefulness of preoperative irradiation in the treatment of endometrial cancer. Clinical effects of radiation are best demonstrated in relation to certain characteristics of the natural history of the disease. Prognosis can be predicted in a general fashion, but the result obtained in an individual patient can be evaluated only by observation over a period of time. It is important, therefore, that experience gained in groups of patients be applied in the treatment of each individual.

The most important factor in prognosis for any cancer is stage of clinical advance. Endometrial cancer is no exception. We do not have for stage-grouping a method that approximates the precision attained in cervical cancer. In the selection of clinically operable patients there will be inescapable errors. It is to be admitted that such cases will be few in number. For the series reported here only four of the 103 patients subjected to hysterectomy were found at operation to have extension outside the uterus. Only one of those patients survived a five-year period free of recurrence, and that individual received preoperative irradiation. Operability rate for the entire series is 52.3 per cent. Application of hysterectomy to a higher percentage should incur risk of attempting to treat surgically a higher percentage of patients with extensions.

Among other factors that may affect prognosis is size of the uterus. Explanation of the adverse effect of uterine enlargement can be made only upon a speculative basis. In discarding the four patients noted at surgery to have extension, we found among the remaining ninety-nine, treated with or without preoperative irradiation, that the uterine cavity measured less than 12.0 cm. depth in sixty-five, and more than 12.0 cm. depth in thirty-four. The five-year survival among those with smaller uteri is 83 per cent. Among those with larger specimens it is 47 per cent. Mention should be made of the fact that a uterine cavity of 12.0 cm. depth is not within limits of normal range, but there can be little disagreement that measurements in excess of that length represent en-

largement. We have not demonstrated in our series a significant improvement for preoperative irradiation in the treatment of uteri of the smaller size. A survival rate of 87 per cent was attained in comparison with one of 79 per cent for hysterectomy alone. Method of radium treatment, by intra-uterine tandem or by insertion of multiple capsules, made no difference in clinical results. Among the larger uteri, however, the preoperatively treated patients present a survival of 52 per cent, but only three of the nine patients treated by hysterectomy alone are alive and well. In the group of patients with enlarged uteri the technique of radium treatment is found to have a definite relation to end results. Introduction of radium by multiple capsules resulted in survival of 63 per cent. It cannot be stated that the packing technique for radium treatment is independent of uterine size in so far as end results are concerned, but there is evidence that adequate preoperative irradiation will advance clinical results in patients with enlarged uteri to a level that approaches that obtained in smaller organs. It is probable that the statistical values given above would be modified in one or another direction by adding for consideration the effect of extent of tumor. The series here is inadequate in number for breakdown into smaller categories.

In spite of the indefiniteness some authors have found for effect of tumor differentiation, broad classification of patients here reported into differentiated and undifferentiated forms show definite relation to end results. For the entire group of 103 clinically operable patients there are 65 presenting lesions interpreted as differentiated, and of that number, fifty-three, or 81 per cent are alive and well at the end of five years. For the thirty-eight patients presenting undifferentiated tumors the survival is only eighteen, or 47 per cent. Preoperative irradiation is not demonstrated to improve results among differentiated lesions. The value shown for that method is 29/38, or 76 per cent. For hysterectomy alone the result is 24/27, or 88 per cent. A different circumstance is shown for undifferentiated tumors. With preoperative irradiation the value is 13/22, or 59 per cent, and for surgery alone it is 5/16, or 31 per cent. These results were given before in discussion of Table IV. The total results given in that table fail to demonstrate improvement for preoperative irradiation. That has been the experience of other authors. The question is complex due to the number of factors affecting prognosis, and a much larger number of patients is required for simultaneous

consideration in a total series of all known factors including stage, uterine size, histology, and method of treatment. It was demonstrated earlier that upon the basis of uterine size the group treated by hysterectomy alone presents a better prognosis than those given the combined treatment. Patients treated by hysterectomy alone also presented a better prognosis upon the basis of stage of advance because several individuals had very small lesions discovered unexpectedly after operation for various benign conditions. It is obvious those factors may mitigate against making clearly defined conclusions upon the basis of total results in a series of the number here given. Collection of statistics now being undertaken by the International Committee should be of considerable value.

The most significant factor in prognosis is control of tumor within the uterus. In clinically operable patients data upon that problem can be taken only from those given preoperative irradiation. The study might be extended to groups treated by irradiation alone by performing curettage. As was noted in tables shown above, a total of forty patients were found to show evidence of tumor control. Survival rate for those individuals is 87 per cent. Among the twenty with residual tumor only 35 per cent survived. None of these with persistent cancer would be expected to survive if hysterectomy were omitted. That fact alone establishes surgery as the basic therapeutic procedure. If, however, control of tumor can be gained by preoperative irradiation, then a marked increase in survival rate is to be expected. Average incidence of tumor control, as measured in routine sections made for postoperative diagnosis, is 66 per cent. Method of radium treatment is important. Use of an intra-uterine tandem has resulted in control in less than half the patients treated. Insertion of multiple capsules produces that effect in about three-fourths of the cases. Size of the uterus affects response to irradiation applied by tandem, but the packing technique is largely independent of that factor in as far as tumor disappearance is concerned. Tumor differentiation is of importance. As was noted earlier a 70 per cent control rate was obtained in differentiated forms, but only 60 per cent in undifferentiated varieties. Finally, the amount of radiation reaching the tumor, as well as the period of time over which the application is made, is of determining effect in regression. In the attempt to arrive at an amount of radiation apt to be lethal for endometrial cancer, we have estimated tissue dose in a few more recently treated patients not

included in the series presented here. Expression of dose as an average of 3 points at 1.5 cm. depth to endometrium indicates that more than 7,000 gamma roentgens delivered within a period of about seven days are required for complete regression. That level of dose and intensity has not often been attained in the combined treatment employed during the 1930-1947 period reported here.

In conclusion it can be stated that the natural history of endometrial cancer mitigates against a survival rate in excess of 65 per cent for hysterectomy alone in clinically operable patients. The principal factors known to affect prognosis include stage of advance, size of uterus, and degree of differentiation in the tumor. Prognosis is excellent for early lesions that are well differentiated and occurring in uteri of normal size. If, however, the uterus is enlarged or the tumor undifferentiated, the probability of cure by hysterectomy alone is about one in three. In those instances the use of preoperative irradiation will double the expectancy for survival. The effectiveness of radiation will vary according to dose and intensity. It is apparent that large amounts are required, and administration of that dose necessitates use of x-rays and radium. A more effective distribution of radium radiation is attained by insertion of sources individually to fill all the available space within the uterus. With carefully planned preoperative irradiation one can expect disappearance of tumor within the uterus in about three-fourths of all patients treated. Survival of those individuals is on the order of 85 per cent.

The mechanism by which preoperative irradiation improves clinical results is vague. Much of our present knowledge is based upon observations made by Dr. Ewing. In the absence of full explanation of all phenomena involved, we shall be more successful in treatment if all clinically operable patients are irradiated before surgery is performed rather than select only certain cases for those procedures. It is to be noted, however, that our immediate problems are not so easily solved. Administration of amounts of radiation that appear necessary may result in sequelae that delay operation or increase morbidity. Hysterectomy is the definitive procedure, and it may not be possible to superimpose upon the trauma of surgery the injury accompanying an amount of radiation apt to be lethal for all endometrial cancers. Observations made in conjunction with use of the combined treatment are directly transposable to treatment by irradiation alone in the substantial numbers

of patients not suited to surgery. There is immediate need for greater detail in data upon the effect of clinical stage of advance. General use of a practical stage-grouping for endometrial cancer will facilitate investigations.

Exploration of those confused and rather fluid problems would surely have appealed to Dr. Ewing, and for that reason it is hoped that this presentation will be accepted as another acknowledgement of our appreciation for his life and his work.

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SOCIAL CONVICTIONS AND CLINICAL PSYCHIATRY*

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THE doctor today, regardless of some of his personal and professional failings which may be both conspicuous and numerous, still remains the symbol of self-sacrifice and devotion to duty. Neither the public nor the medical profession seems to be easily dissuaded from the lingering conviction that the doctor may not refuse to treat an ailing person merely because the person is too poor or the doctor is too tired. In the mind of the man in the street the doctor should not be too poor, but neither should he be rich, because if he shows any degree of affluence he may be suspected of exploiting his patients. The doctor may never be tired, nor sleep too much, and he should always be ready to "take a call."

There are other unspoken demands made upon the doctor. He must not spend too much time with his own wife and family, although he ought always to be charitably ready to take profound interest in the wife, husband and children of other families. The doctor should not be a politician; a doctor who takes active part in politics is looked upon with the same suspicion which is accorded to a priest who enjoys social entertainments.

We know that in fact all these demands are not strictly imposed or strictly respected. We have had medical doctors who were politicians enough to be elected to the United States Senate, and we have had and have doctors whose social life is far from interfering with their professional reputation. Yet the demands exist, and they make themselves felt every now and then. The Hippocratic Oath is still looked upon not only as an oath of office but more as an act of self-dedication and consecration. This attitude of both the public and the doctor, no matter how couched in the present-day idiom of automobiles, typewriters and politics, is a sign of how deeply rooted within us is the tradition that medicine originated in priesthood. No matter how modern and sophisticated we may appear, there lives within us a mixture of

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prejudice and jealous faith which reflects some of the old demands of the days of Hippocrates nearly twenty-five centuries ago, of the days of Rhazes nearly one thousand years ago, demands that a physician remain a physician and indulge in no drink, or music or poetry.

Ours being a practical age, we would be a little astonished if a physician refused a cocktail on the grounds of professional ethics, and we vouchsafe the poetry of an Oliver Wendell Holmes and the novels of a Weir Mitchell. Yet the fantasy of spiritual perfection perseveres in our image of a physician. This does not mean necessarily that we consciously and always idealize our doctors and imagine them perfect. On the contrary, we are prone as often as not to criticize them for their failings, which criticism is often but an expression of an ideal betrayed, or an idealization deceived. This is particularly true of the general attitude toward the psychiatrist. We resent in him anything which appears to us neurotic. A psychiatrist is not supposed to be "subjective" or low spirited, or too enthusiastic. If we condense all those things which a psychiatrist ought and ought not to be, we shall obtain an image of an Olympian middle-of-the-roader, a generous, outgoing, yet great, silent man, a person who feels deeply everything for everybody and has no deep feeling for anything. A paradoxical image, of course; age-long fantasies are always paradoxical and inconsistent with truth. But history knows a few medical figures who were of truly heroic proportions and who yet remained inconspicuously detached, happily or luckily little and quiet as compared with the vastness and noisiness of the events around them. Philippe Pinel was such a person. He lived through the bloodiest days of the French Revolution, the militaristic rise and fall of Napoleon, the pomposity of the Restoration. Yet he remained a doctor to his patients, a citizen who fought the prejudices of the Jacobins against the mentally sick; he wrote steadily, and continued his work of organization. He warded off the imperial distinction which Napoleon offered him, and escaped the decorous recognition with which he was threatened by the advent of Louis XVIII. To be sure, Pinel was unique. He was an exception of the first order. The average doctors of his day must have fared less well, and certainly most of them must have been engulfed in the social and political struggles of their day.

One need not, especially in our industrial civilization, wait for some severe social crisis to see how the physician, particularly the psychiatrist, becomes involved in the issues which are pointed up by the given

crisis. But it so happens that the twentieth century has been one of successive crises which in our generation have reached global dimensions, and we can no longer indulge in our old fantasy of Olympian objectivity and equanimity. For in general medicine and surgery there are still stretches of activity which are characterized by what Oliver Wendell Holmes called Medical Christianity. The surgeon, for instance, cares little whether a given gallbladder duly filled with stones and duly infected belongs to a murderer, a justice of the Supreme Court, or a Communist official. The gallbladder must be removed, and the surgeon removes it. Who would think of blaming or approving of such a surgeon, of speaking of him as a person who aids and abets crime, or serves the ends of justice, or favors Communism? Moreover, the surgeon himself would hardly feel guilty for having performed a cholecystectomy on a criminal, nor would he feel particularly virtuous for having taken out the appendix of a judge, nor would he consider himself a fellow traveler whose conscience is tainted with pink because he operated on a Communist official.

The psychiatrist finds himself in a different and singular situation. Not only do district attorneys and judges and juries suspect him of being strange and not a little anti-social when he testifies to save a murderer's life; the psychiatrist himself feels not a little squeamish if he says something about the mental condition of the defendant which might ease the defendant's fate. He feels as if he sides with the criminal and therefore in part condones the crime. All this may not be crystallized and precise in the psychiatrist's mind, but his usual discomfort in such situations means just this. I do not know whether the psychiatrist would feel particularly virtuous in treating a jurist, but there is no doubt that he would feel troubled, and quite deeply, if he were called upon to treat a Nazi or a Communist. As to the "world," if "they" knew that he had a well known Communist or Nazi as a patient, they would wonder "how he does it."

In other words, the psychiatrist constantly finds himself in the very midst of those conflicts above which he himself cannot easily if at all rise, and beyond which he is hardly able to reach out without settling in his own mind a number of issues—social, political and religious. All this creates a number of complex and confusing problems both for the psychiatrist and for his patient, and particularly of course in times of great cultural crises.

Take as an example the situation in the Soviet Union. To be sure, any citizen of the Soviet Union is required by the very nature of the totalitarian state to assert his loyalty to the prevailing ideology and to accept the basic tenets of the social philosophy of the Soviet State. Yet the surgeon or the internist is not called upon to explain the use of certain sutures, or the physiology of diabetes, in terms of economic determinism. The psychiatrist, on the other hand, finds himself enmeshed in the cobwebs of the prevailing social philosophy. Thus an old colleague of Charcot, a great neurologist and a general in the Tsar's Army Medical Corps, the master-neuroanatomist and neurophysiologist V. M. Bechterev sought in his old age to give point to his theory of conditioned reflexes by pronouncing this theory to be well adapted to the Hegelian-Marxian dialectic materialistic philosophy. Consciousness, its very existence, has been loudly and emphatically denied. In this denial the Marxian materialists unbeknown to themselves became metaphysicians by calling consciousness merely a "higher form of the organization of matter."

It is very difficult under these psycho-social circumstances to be an objective clinical psychiatrist. For in addition to the social philosophy which appears to have become both a peremptory and mandatory part of psychiatry, the psychiatrist is impeded clinically by the necessity of observing only those symptoms which would serve to corroborate that philosophy, or to refute the opponents of it. Psychoanalysis is rejected not because its empirical findings are tested and found incorrect, but because those findings are judged in advance as non-acceptable since Freud is considered a metaphysician, an idealist and individualist—all designations of scientific and even moral opprobrium, because only the practical materialist and socialist are supposed to be endowed with the gift of begetting the truth. Clinical psychiatry under these circumstances regresses to that historical level at which it was some four hundred years ago, when it just began to try to become a true branch of clinical medicine. This was the level at which the established order of things refused psychiatry the right to become scientifically independent; it insisted that psychiatry remain inseparably fused with the religious philosophy and social prejudices of the times.

I am not unaware of course that the type of retrogression of which I speak here is not absolute. A great many scientific works are being pursued in the Soviet Union today, but the principle of having a social

philosophy officially dominate a branch of clinical medicine is a deadening principle whichever way you may look at it.

However, this process of retrogression of clinical psychiatry is not limited to the Soviet Union. In the Soviet Union today this retrogression is apparently imposed by the policy of the state from without, as it were. In other countries, and even in ours, psychiatry shows some similarly discouraging signs—and the pressure seems to be coming from within, with no interference on the part of the state. Let me cite to you a short excerpt from a recent issue of a medical journal. "Most people," state the psychiatrists who contributed this article, "do not realize that competition is a biological characteristic fundamental to the behavior of mankind. This blindness to reality seems to perpetuate socialism and communism. . . . The refutation of the concept of psychopathic personality by psychoanalysts and by communists, and the denial of the Mendelian Law by Lysenko is evidence that our culture is now standing upon an interesting threshold—who knows? Maybe the Dark Ages are again upon us." . . . And further: "There is a communistic, a psychoanalytic and a socialistic contention that a properly controlled environment would have changed the outcome of anti-social children. This contention supposedly justifies a deluge of social workers to take care of family problems. Once again we hear the accusation, 'You don't love our children or society enough,' you must share your possessions to prove this love and affection.

"Such is reflected today as the greatest problem of our American democracy; Social Security, unemployment compensation, and old age pensions are manifestations of a social psychopathy."[1]

It is granted that the above is a very extreme expression of a very extreme opinion in a manner of quite extreme confusion. Yet even after we make all these allowances, we shall admit that this opinion in some way reflects a psychological trend in present-day psychiatry which may not be overlooked or underestimated. For under the influence of the present-day critical events of political, social and spiritual tensions, two things in the field of psychiatry have become especially accentuated.

1. Not only is the psychiatrist called upon to use his skill in the treatment of the victims of our conflicts wherever they are found, in the army, in industry, in our society in general, but also he is asked to use his skill in direct participation in defense efforts, in psychological

1 Coyne H. Campbell, Harold G. Sleeper, "Socialism and Psychopathy." *The Journal of the Oklahoma State Medical Association*, Vol. 45, No. 4, April 1952, p. 138.

warfare. In other words, the psychiatrist is called upon to become a combatant possessing special medico-psychological skill, rather than to remain merely a doctor whose job is to care for the sick.

2. The psychiatrist is called upon, or as a result of cultural pressures he volunteers, to use his clinical knowledge in order to preserve or to salvage various concepts of social values which seem to be threatened by the ever-mounting crisis. The psychiatrist then seeks to transpose his psychiatric clinical concepts into social ones; these efforts are impressive in their daring but highly confusing as to practical results or scientific validity. Thus it has come to pass that, depending upon the camp he happens to be in, the psychiatrist will "recognize" the psychopathic and communistic traits in psychoanalysts, or he will dub the communist or the fascist a psychopath and claim to have discovered a well-defined, anti-Semitic or authoritarian personality.

What happens in this confusion is this: the clinical psychiatrist, as a result of the mounting of his own awareness as a citizen, as a child of his age, as a son of his country, as a defender of democracy, becomes engulfed in the maelstrom of social passions and recognizes as the true sons of democracy only mature, adult, non-neurotic individuals. He is apt to assert that the non-democratic individuals—the Communists, the Fascists, the Nazis—are all immature, infantile, neurotic, psychopathic individuals. Thus, clinical psychiatric terminology becomes little more than bitter namecalling in the midst of social passion and prejudice—a far cry from the objective, clinical, humanistic Medical Christianity which was so much extolled by Oliver Wendell Holmes.

I would not want to give the impression that the clinical psychiatrist can or must be completely outside the social struggle and shun any of the issues which confront us today. But I do want to say, and as emphatically as I am able to, that the psychiatrist who aids and abets the cure of society of its alleged social psychopathies becomes more a slave of the ideology he happens to accept (from Jefferson to Marx), and must therefore sacrifice both his scientific objectivity and his medical humanism. To be aware of the nature and intensity of the cultural struggle around us, to be a part of it, is one thing; but to be an active servant and partisan of this struggle is another thing—it is something that has really nothing to do with the curative art.

What is the psychiatrist to do? It is not easy to give too definite an answer. I, for one, found it impossible on some occasions to treat a

sincere Nazi sympathizer in the midst of Hitler's terror. I had to interrupt the treatment because I was unable to control my sense of revolt and revulsion. Now, when the psychological distance from Nazism has been established, I would not find it difficult to treat an anti-Semite or Nazi. The same I found to be true with some convinced adherents of Communist political philosophy. In general I found it not difficult to treat certain patients of fascist or communist leanings whose neurosis was colored by their social philosophy, but I did find it difficult and most of the time impossible to be confronted with a rigid social philosophy, well crystallized as if independent of the neurosis itself. I believe that the psychiatrist ought to be able to assess his own social susceptibility and prejudices without shame and without self-righteousness, and proceed with his therapeutic task in those cases in which he can in his own eyes preserve his own psycho-social integrity. Often it is difficult to assess our susceptibilities and prejudices, particularly in times of crises during which psychiatrists cannot help but be directly or vicariously involved. Yet an assessment of one's own psycho-social inventory, difficult and imperfect as it often may be, cannot help but preserve the medical tradition of psychiatry. Any other form of squaring ourselves with the problem thus far offered does injury to psychological medicine and to the professional integrity of the psychiatrist.

One of the suggestions for solving the difficulty is that we wear quite honestly and candidly the mask of supreme objectivity—as if nothing really disturbs us, nothing that anyone may do or fail to do. This mask is frequently imposed upon us by the public who picture the psychiatrist as an immovable rock of wisdom and detachment. True, the collective tongue of the public is always in its collective cheek when it raises psychiatrists to these non-existent heights of objectivity. Yet both the public and psychiatrists are apt to become seduced by this type of fantasy and behave as if it could be a reality.

Another way to escape the difficulty, recently suggested in some quarters, is for the psychiatrist to refuse completely to participate in any controversial social and political undertakings. It is suggested that the psychiatrist walk alone, so to speak, in a sort of movable ivory tower of splendid isolation, away from yet in the midst of the world. Such a self-imposed cleaving away from the main stream of life is to say the least impractical. But it is also very dangerous, because if successful it would remove the psychiatrist from the human contacts without

which he cannot be a psychiatrist, and if a failure, it would force the psychiatrist into an atmosphere he does not approve. He would then be resentful and therefore unable to be a psychiatrist; for one cannot be a psychiatrist while carrying a sense of resentment, any more than one can be a surgeon while suffering from a blood phobia.

The above outline of the difficulties with which the psychiatrist is confronted today might give the impression that there is no solution, no adequate alternative to be found. To some extent this is true. As long as the cultural crisis is acute, it is impossible to prescribe any sure cure. There will always be Pinels, Esquirols, and Isaac Rays—men who can somewhat rise above and yet remain a part of human struggle. But there will always be the majority of us who become a part of the failings and failures of our age, like a Jean Fernel or a Felix Platter. These men were great clinicians and master medical minds but unable to rid themselves of the prejudices of their day. They hated witches and sorcerers. Fernel refused to give medical aid to suffering alleged witches; Platter would study the mentally ill with miraculous tenacity and apparent objectivity, but he was unable to consider that their place was in a hospital because their illness he believed was of the devil. The history of medicine, and particularly the history of psychiatry, knows many examples of such failures, for they were numerous, and at times they were the majority of the medical profession. But in the end it was a Johannes Weyer who won the day and brought psychiatry to the clinical and curative level to which it had for so long struggled to rise. In other words, the failures, no matter how numerous they may be, are after all but as much a sign of the times as the cultural crises themselves.

In the light of this historical perspective one must admit that psychiatry just now is going through a period of not inconsiderable flux because it is so often engulfed by the crises of our day. That which is most important in psychiatry and to the practicing psychiatrist—the human individual, the person, the integrated human being—seems to be overshadowed by more pressing things. The advent of social cures, electric shock, operative procedures are but a reflection of the "total push" of our time in the direction of mass action, mass behavior, mass drives, mass production and mass integration. Clinical psychiatry cannot escape this tidal wave in the Western cultures any more than in the Soviet Union. However, should a Johannes Weyer arise in our Western culture—and he would probably have a very difficult time as Weyer

himself had—he would still have his chances to survive, even as Johannes Weyer and his work succeeded in surviving despite the fact that he lived in a dangerous age of bonfires and ruthless scorn for certain truths. For as long as there is, be it ever so formalistic, the recognition of the value of the individual in man, man cannot be lost. And as long as the value of the individual is preserved, clinical psychiatry will not only survive but may be the only clinical scientific discipline which will make a decisive contribution to the solution of the present-day crisis.

This is why the psychiatric clinician today, whatever his social bent, finds himself more and more called upon to solve the problems of the relationship between psychiatry and moral and religious values. Those psychiatrists who are engulfed by the mass mentality of today do not seem to seek for a solution of this problem. In fact, they deny the need of introducing moral and religious values into the scope of their clinical perspectives. These psychiatrists make their own contribution to the solution of the problem in that they point up the acuteness of our cultural crisis by succumbing to sociological, mass therapeutic trends. They, by the very virtue of the stand they take, will deal with statistics and common denominators. In other words, they will of necessity seek that which was decried by Oliver Wendell Holmes as early as the mid-sixties of the last century, when he exhorted young medical men to avoid becoming fascinated by the vogues of averages. The average, the disindividualized common denominator, is an important factor in the impersonal disindividualized world of crises in which we live. At the same time, this very rise in importance of the common denominator contains the seeds of the fall of this method of approach, since the common denominator is derived from masses of men, and man cannot survive except as a self-conscious, autonomous individual.

There is no doubt that we are now going through a period of disindividualizing our lives, and therefore we are not yet able to develop fully a true, humanistic clinical psychiatry. But then, historical perspectives do not appear to visualize the human world as functioning like a human ant-hill. The statistical, common denominator method is self-limited, whereas the individual as the unique and only bearer of human life and its values will sooner or later assert his autonomy and his importance regardless of the stifling low level to which he is pushed by our critical times. And with the renewed rise of the individual, the renaissance of humanistic psychiatry will become inevitable.

MEDICAL CARE AND SOCIAL POLICY IN SEVENTEENTH CENTURY ENGLAND*

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WHEN Tudor England moved out of the Middle Ages, one result of the disappearance of the old order was an increase in poverty.[1] This problem was a matter of grave concern, for poverty was regarded as a potential danger to the security of the State. Various acts designed to deal with the poor were passed during the sixteenth century, and these measures were finally consolidated in the Elizabethan law of 1601 (43 Elizabeth, Chapter 2), which remained the basis of English poor law administration for over two centuries.

Administrative responsibility for the relief and government of the poor was assigned to the parish. As the unit of ecclesiastical administration, it was found to be a convenient division for local government. Thus when it became necessary to make systematic provision for the poor, the parochial machinery was adapted to the purpose; and the relation between the poor and the parish became peculiarly close and intimate.

While the law of 1601 makes no specific mention of health matters, it was intended to relieve the "lame, impotent, old, blind, and such other among them being poor and not able to work." As time went on, however, this simple statement was expanded in practice to include the provision of medical and nursing care.

It appears probable that the policy laid down in 1601 was followed until the outbreak of the Civil War. Wartime conditions and official neglect led to a disorganization of the poor law administration. This situation was further aggravated by the necessity of providing for wounded soldiers and their dependents.[2] These urgent and exceptional matters demanded attention, and emergency measures were taken to deal with them. In the main, however, poor law policy under the Com-

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monwealth followed along lines previously laid down. Nevertheless, a changed attitude toward the problem of poverty was developed during the period.

There is small doubt that during these years poverty came increasingly to be regarded as a disgraceful social disease. In this respect, the Interregnum anticipated the earlier eighteenth century. This position may in considerable measure be attributed to the influence of Puritanism, that is, the core of common values accepted by the Protestant sects of seventeenth century England. Within this value system certain doctrines are fundamental, among them predestination and justification through good works. Intimately associated with these theological values was an insistence on diligence and industry as necessary and worthwhile, with definite stress on utilitarian considerations. Richard Baxter in his *Christian Directory* justified this principle in these terms: "The public welfare, or the good of the many," he says, "is to be valued above your own. Every man therefore is bound to do all the good he can to others, especially for the church and the commonwealth. And this is not done by idleness, but by labour! As the bees labour to replenish their hive, so man being a sociable creature must labour for the good of the society which he belongs to, in which his own is contained as a part." [3] Furthermore, since methodical, constant labor makes possible success in one's calling, and such success is a sign of salvation, constancy in labor becomes a worthwhile end in itself. From this viewpoint poverty was an abomination, due to lack of moral stamina and systematic application.

But while poverty was regarded as an individual vice and condemned on ethical grounds, it was also discovered to be a potential source of profit to the state and therefore a public convenience. Projects for dealing with the poor and for utilizing their labor were proposed during the Commonwealth, and the number of these proposals increased greatly in the decades following the Restoration. Apparent in these proposals is a mingling of motives, among which mercantilistic considerations and the prospect of profits are prominent. With an insight which is quite remarkable, efforts were made to compute the national cost of idleness, and elaborate calculations were developed as to the increase in national wealth which would result if England's poor were made productive.

Among the proponents of such schemes some were aware of the

health needs of the poor. In 1641 there appeared *A Description of the Famous Kingdome of Macaria* by Samuel Hartlib. In this Utopia, Hartlib was interested mainly in proposals for social and economic reform. A special feature of Macaria, however, is a "College of Experience, where they deliver out, yearly, such medicines as they find out by experience; and all such as shall be able to demonstrate any experiment, for the health or wealth of other men, are honourably rewarded at the publick charge."[4] Hartlib also felt that parish priests would be more useful if they acquired some knowledge of healing, and he pointed out that in Macaria "they think it as absurd for a Divine to be without skill of Physick, as it is to put new wine into old bottles." These comments should not be considered simply as quaint conceits, but must rather be regarded as serious proposals to improve the provision of medical care, especially to the poor. In Caroline England and under the Commonwealth the number of trained physicians was small. During this period medical practitioners more and more formed a group marked by steadily increasing status and remuneration so that their services generally were not available to the poor.[5] At the same time, there is evidence from parish registers and other sources that the clergy did provide home remedies and advice on medical care.[6]

Clearly Hartlib's proposals were in line with these contemporary realities and needs. Evidence for such a view is provided from several different directions. The existence of a medical care problem is confirmed by John Cooke, a conservative and a former member of Charles I's government. In his pamphlet *Unum necessarium*, published in 1648, Cooke pleads for relief of the poor including free medical service.[7] A further indication of the apposite and constructive character of Hartlib's scheme is provided from the opposite end of the political spectrum, from the extreme left wing of the Puritan movement. In 1652 there appeared a book entitled *The Law of Freedom in a Platform or True Magistracy Restored*. The author was Gerrard Winstanley, spokesman for the group called Diggers or True Levellers, an offshoot of the popular democratic party known as the Levellers.[8] This book set out a plan for an agrarian socialist commonwealth. In Winstanley's plan a prominent place was assigned to the clergy. To a large extent the function of the minister was to be an educator. Among his duties would be the instruction of his parishioners in the arts and sciences, including medicine and surgery. It may be that Winstanley was acquainted with

Hartlib's suggestion about the clergy and adopted it.

Meanwhile, Hartlib had developed another scheme to deal with the needs of the poor. He proposed, in 1647, the establishment of an Office of Addresses "for the Relief of Human Necessities."[9] This projected Office would function as a labor exchange, information bureau, and a place for the transaction of commercial business. Here would be maintained various registers, of which the most important would deal with the needs of the poor. These would include a list of physicians willing to give their services gratis. Efforts to set up such offices were made in 1650 by Henry Robinson in London, and about the same time in London and Westminster by Hartlib himself. It is not clear, however, whether lists of physicians were maintained at any of these offices.

In 1648, there was published in London a small book of thirty pages entitled *The Advice of W. P. to Mr. S. Hartlib for the Advancement of Some Particular Parts of Learning.* The author was William Petty, then "twenty-four years of age, a perfect Frenchman, and a good linguist in other vulgar languages, besides Latin and Greek; a most rare and exact anatomist and excelling in all mathematical and mechanical learning. . . ."[10] Directly inspired by Hartlib, this booklet presented several proposals for the reform of education. Petty's proposals are in line with a trend found among the Puritans of both the right and left, namely, a desire to apply knowledge to the immediate and practical needs of society. Education is a matter of vital concern to all revolutionary parties, and the leaders and spokesmen of the English revolution were fully aware of this fact. Indeed, the advent of the Long Parliament was the signal for an outburst of discussion and action on the reform of education.[11] The positive proposals for reform reflect the chief aspirations of the rising English middle class—utilitarianism, individualism, and the experimental philosophy. These ideals find concrete expression in Petty's scheme. Of special interest is his proposal for a hospital where physicians and surgeons would give and receive instruction. The hospital would be fully equipped with an anatomical theater, a chemical laboratory, an apothecary shop, a garden and a library. Among the chief personnel would be a physician, "skilled at large in the phenomena of Nature," who "shall either dissect, or overlook the Dissection of Bodies dying of Diseases; and, lastly shall take care that all luciferous Experiments whatsoever may be carefully brought to him, and recorded for the Benefit of Posterity." In addition, there

would be an assistant physician who would maintain suitable records on all patients, a surgeon, and an apothecary who would be in charge of the garden. The young medical student would learn the practical side of his profession by accompanying the members of the medical staff from patient to patient.

More clearly than anyone else, perhaps, Petty represents that combination of utilitarianism, commercial drive and experimental philosophy which characterized the approach to social problems in the period following the Restoration and during the eighteenth century.[12] Petty's proposals for educational reform and advancement of knowledge stem in a straight line from Bacon's *New Atlantis* by way of Hartlib's *Macaria*, and point to the enthusiastic promulgation of elaborate projects for commercial undertakings, technological innovations and social reforms during the later seventeenth and earlier eighteenth centuries. This penchant for projects when applied to the burning issue of the poor was to be one of the significant factors determining the framework of theory and practice within which social problems of health would be viewed in the eighteenth and early nineteenth centuries.

Petty is representative, however, not only as a projector, but equally as a pioneer in the quantitative study of social phenomena. The application of the numerical method to the analysis of social problems was a development of first-rate importance, and destined to prove extraordinarily fruitful for the study of the social relations of health and disease. Petty was convinced that social and economic problems could be dealt with most effectively in terms of functional analysis and measurement, what he termed political arithmetic. His employment of this method was not merely a happy chance; he was keenly aware of the end he wished to achieve and of the means by which he proposed to do so.

In the preface to the *Political Anatomy of Ireland*, Petty says: "Sir Francis Bacon, in his *Advancement of Learning*, hath made a judicious parallel in many particulars, between the body natural, and body politic, and between the arts of preserving both in health and strength: and it is as reasonable, that as anatomy is the best foundation of one, so also of the other; and that to practice upon the politick, without knowing the symmetry, fabrick, and proportion of it, is as casual as the practice of old-women and empyricks. Now, because anatomy is not only necessary in physicians, but laudable in every philosophical

person whatsoever; I therefore have attempted the first essay of political anatomy." [13]

The means for such study is political arithmetic. Petty's posthumously published work, *Political Arithmetick*, describes it in these terms: "The method I take," he says, "is not yet very usual; for instead of using only comparative and superlative words, and intellectual arguments, I have taken the course (as a specimen of the political arithmetic I have long aimed at) to express myself in terms of number; weight, or measure; to use only arguments of sense, and to consider only such causes, as have visible foundations in nature; leaving those that depend upon the mutable minds, opinions, appetites, and passions of particular men, to the consideration of others."[14]

While Petty coined the term political arithmetic and indicated the significance of a quantitative study of social fact, the most valuable pioneer work in this area was done by his friend John Graunt (1620-1674), a London haberdasher. Graunt's classic contribution appeared in 1662 and was called *Natural and Political Observations . . . upon the Bills of Mortality*. While Graunt's work was not without antecedents, he was a statistical pioneer blazing a new trail.

Far back in the Middle Ages, numerical data had been collected for specific purposes. The Domesday Book, for instance, provided a complete review of the resources of the kingdom conquered by the Normans, but no statistical use was made of this information.[15] Later, political writers, such as Machiavelli, made use of figures, and mathematical calculations began more and more to be employed in public affairs, particularly by rulers in making surveys of the resources and revenues of their domains. Typical is the survey carried out by a German prince, Wilhelm IV, Landgrave of Hessen-Cassel, who ruled from 1567 to 1592. At the same time, advances in mathematical knowledge and expansion of scientific interests intermingled with these political and economic influences to bring about a still greater employment of numerical information. Two other streams of influence reinforced this trend. One was an increasing awareness of regularity and order in the world of human affairs. The perception of law and order in the physical realm undoubtedly provided a basis for this view. Recognition of an orderly universe made it seem logical to infer that the same might be true for society. The other stream of influence came from the effects of everyday thought and practice. Throughout this period, more and

more people were learning how to do simple calculations and make measurements. This spread of the knowledge of elementary mathematics helped to prepare the way for the numerical study of social facts.

Thus it was not a matter of chance that a man like Graunt began to search for mathematical regularities in such human events as births and deaths, the incidence of disease, and related matters. Nor was his search in vain, for Graunt brought to light a number of very important facts. In the first place, he demonstrated the regularity of certain social and vital phenomena. Thus he noted "That among the several casualties some bear a constant proportion into the whole number of burials; such are chronical diseases, and the diseases whereunto the city is most subject; as for example, consumptions, dropsies, jaundice, gout, stone, palsie, scurvy, rising of the lights or mother, rickets, aged, agues, fevers, bloody flux, and scowring: nay, some accidents, as grief, drowning, men's making away themselves, and being kill'd by several accidents, &c. do the like; whereas epidemical and malignant diseases, as the plague, purples, spotted fever, smallpox and measles do not keep that equality; so as in some years, or months there died ten times as many as in others."[16] Secondly, Graunt was the first to note the excess of male over female births as well as the eventual approximate numerical equality of the sexes. Thirdly, he called attention to the excess of the urban over the rural death rate.

In making these discoveries, Graunt clearly demonstrated the usefulness of the statistical approach which Petty advocated. But while he indicated some of the social relations of vital phenomena, as well as the social significance of his studies, Graunt did not pursue further this aspect of the matter. It was precisely in this area, however, that Petty made his most significant contribution.

The inspiration of Petty's interest in political arithmetic is not far to seek. He was concerned with all sorts of practical affairs: fiscal matters, trade, population, education, the plague. Full of the idea that numerical data could throw light on such problems, he employed figures and calculations wherever he could. At all times, however, the focus of interest is not on calculation for its own sake, but always in relation to the specific political, economic or social problem involved. This characteristic orientation is clearly revealed whenever he deals with matters of health, in his discussions of population, and in his various statistical proposals.[17] Throughout his numerous published and un-

published writings occur schemes to increase the power and prestige of England.[18] As an essential element of these schemes, Petty urged repeatedly the collection of statistical data on population, trade, manufacture, education, diseases, revenue and many other topics. The breadth of his approach is strikingly illuminated by his "Method of enquiring into the state of any country." This memorandum outlined a complete scheme for a political, economic, social and health survey. Among the topics listed are not only a census of the population, and the nature of the public revenue, but even such questions as "What are the bookes that do sell most."[19]

Within this broad frame of reference Petty was able to grasp clearly the social relations and implications of a number of health problems. Thus, he recognized that it was not enough simply to acknowledge natural fertility and population as major conditions of national prosperity. The acceptance of this premise went hand in hand with the responsibility for removing impediments to the full development of these resources. A major aspect of this responsibility was the creation of conditions and facilities which would promote health, prevent disease and render medical care easily accessible to those who should have it. The achievement of these aims required that medical knowledge be advanced to the greatest degree possible, and Petty pointed out that it is the duty of the state to foster medical progress. "Now suppose," he said, in a lecture given at Dublin in 1676, "that in the King's Dominions there be 9 millions of people, of which 360,000 dye every year, and from whom 440,000 are borne. And suppose that by the advancement of the art of Medicine, a quarter part fewer dye. Then the King will gain and save 200,000 subjects per annum, which valued at 20 £ per head, the lowest price of slaves, will make 4 million per annum benefit to the Commonwealth. Now I consider that the thorough and profound search into the naturall and entire state of animals by anatomy, and into their depraved and vitiated estate by the comparitive and contrasted observations in hospitalls, may in 100 years advance the art of medicine as above said. Wherefore it is not the Interest of the State to leave Phisitians and Patients (as now) to their own shifts."[20]

Almost thirty years earlier, Petty had recognized the crucial importance of the hospital in the training of physicians and in the furtherance of medical research, and to this point he returned again and again. In various connections, he urged the establishment of hospitals. In the

lecture cited above, he commented that "Another cause of defect in the art of medicine and consequently of its contempt is that there have not been Hospitalls for the accommodation of sick people, Rich as well as Poor, so instituted and fitted as to encourage all sick persons to resort unto them—Every sort of such hospitalls to differ only in splendor, but not at all in the Sufficiency for the means and remedy for the Patients health. For by such means the most able understandings might be encouraged, equally with the best of the professions, to spend and to dedicate themselves wholly to this faculty; and a man shall learn in a well regulated hospitall, where he may within halfe a hower's time observe his choice of 1000 patients, more in one yeare then in ten without it, even by reading the best Books that can be written. For, as one may learn to know and distinguish a face better by one minut's Inspection then by reading ten sheets of paper in the description of it, So wee may learn more of sick people by the Joynt assistance of all our sences together than by the lame descriptions of words alone."[21]

Petty supplemented these general recommendations by specific proposals. These dealt particularly with health problems where he felt that the state by establishing hospitals would derive the greatest gain. Thus, in 1687, in "An Essay for the Emprovement of London," Petty proposed "That there bee a Council of Health viz. for the Plague, acute and epidemicall diseases, aged foundlings, as also for persons and houses of correction, and all sorts of hospitalls and women in childbed."[22] Another memorandum composed in the same year suggests a hospital of 1000 beds for London. For Petty, the basic political and economic importance of population was axiomatic. Consequently, any measures to prevent impairment of population by disease and death were matters of high concern. Control of communicable disease, especially plague, and the saving of infant life would, Petty felt, contribute most toward this end. This conviction is reflected in his various suggestions for combating plague, and advocating maternity hospitals. In dealing with the plague, he suggested that the government should consider carefully "what sum of money, and Meanes ought to be prudently ventured for the probable cutting off 3 fifths of this Calamity."[23] Petty recommended the establishment of isolation hospitals, to which plague patients would be removed and where they would receive medical care. To buttress this recommendation, and in general the usefulness of any measures undertaken to combat the ravages of

the plague, he undertook to calculate the economic loss due the disease.[24] Similarly, he advocated the creation of maternity hospitals, having in mind particularly unmarried pregnant women. Petty contemplated that in return for such provision provided by government, the children would become wards of the state and serve it for twenty-five years, thus adding to the labor resources of the country.[25] He also believed that certain other groups in the population were of direct concern to government. These elements comprised the occupational groups esteemed as most productive—farmers, manufacturers, merchants, seamen and soldiers. In his opinion, these occupations "are the very pillars of any commonwealth."[26] In keeping with this point of view are suggestions by Petty that studies be made of occupational morbidity and mortality.[27]

Finally, Petty realized that to achieve these ends an adequate supply of medical personnel would be required. Consequently, he proposed that an analysis be made of the medical need, using methods such as those of Graunt, and then on this basis to calculate the numbers of physicians, surgeons and others necessary to meet this need. In short, Petty proposed that the number of medical personnel be planned and adjusted to meet the actual need for medical care. "As for Physicians," he wrote, "it is not hard by the help of the observations which have been lately made upon the Bills of Mortality,[28] to know how many are sick in *London* by the numbers of them that dye, and by the proportions of the City to finde out the same of the Country; and by both by the advice of the learned Colledge of that Faculty to calculate how many Physicians were requisite for the whole Nation; and consequently, how many students in that art to permit and encourage; and lastly, having calculated these numbers, to adoptate a proportion of Chyrurgeons, Apothecaries, and Nurses to them, and so by the whole to cut off and extinguish that infinite swarm of vain pretenders unto, and abusers of that God-like Faculty, which of all Secular Employments our Saviour himself after he began to preach engaged himself upon."[29]

Petty's views on the social and economic implications of health problems are beyond all comparison the most significant English contribution to this area of social thought prior to the nineteenth century. To get a clear picture of Petty's position it is necessary to piece together numerous separate statements. When this is done, however, there emerges a relatively coherent and logical structure. Essentially a disciple

of Hobbes in his political theory, Petty accepted the thesis that government is justified in carrying out any policy or instituting measures by which national power and wealth would be increased. At the same time, he recognized that while individuals or groups might be harnessed to the needs of the state, public policy should also aim at improving their living standards. Populousness was exceedingly desirable, but the people should also be healthy and happy.

Petty was not alone in dealing with the social aspects of health problems, or in attempting to study them quantitatively. Among his contemporaries and followers these interests were expressed in varying degree and some were keenly alive to the importance of a healthy population as a factor in national opulence. Closest to Petty, perhaps, was his younger contemporary Nehemiah Grew (1641-1712), also a physician, but best known today for his work in plant anatomy. Sometime in 1707 apparently, Grew prepared for Queen Anne a memorandum entitled *The Meanes of a Most Ample Encrease of the Wealth and Strength of England in a Few Years Humbly represented to her Majestie In the Fifth Year of Her Reign.*[39] As the title indicates, this document outlined an economic program to enhance the prosperity and power of England. Grew's focus of interest was the same as Petty's, and his handling of health problems occurs within a similar context. He knew Petty, to whom he refers as "my late Honoured Friend," and frequently mentions Petty's calculations, though he does not always accept them. Like Petty in the *Political Anatomy of Ireland*, Grew couched his discussion in terms of anatomy and physiology. In his opinion the four basic elements in the economic anatomy of England are land, manufactures, foreign trade, and population. Ultimately, however, Grew's program depended on the size and quality of the population, and to this subject he devoted the fourth section of his memorandum. Grew assumed as axiomatic the need for increasing population to provide the necessary labor power. Among his recommendations toward this end, he urged that the state do all in its power to maintain health and prevent disease. Grew emphasized the economic burden of disease, commenting that in economic terms the sick are worse than dead because they become either public or private charges. To make medical care available to all, Grew proposed that the government regulate physicians' fees according to their experience. If this were done the cost of medical care could be reduced and thus made accessible to those who needed it.

Despite their bold and penetrating character, the ideas of Petty and Grew had no immediately tangible results. Their proposals did not lead to a satisfaction of human needs in relation to health, because they were implicitly premised on a type of governmental structure which was even then being discarded. Effective implementation would have required the existence of a well-developed local administrative mechanism operating under strongly centralized control, in a manner comparable to the organizations of France or Prussia. But it was precisely these organs of administration which were then disappearing. After 1660 there was no planned effort to use local officials as efficient organs of a consistent policy.

Cunningham, the economic historian, employed the term "parliamentary Colbertism" to describe this period and its continuation in the eighteenth century.[31] Although this designation is only partly correct, it calls attention to contemporary French developments, and by inviting comparison makes it possible to focus more sharply the characteristic features of English evolution. Colbert created a whole system of administrative regulation under central control, and built up a bureaucracy to keep the machinery in operation. In England, on the other hand, the administrative apparatus which had been developed under the first Stuarts had collapsed and was not being replaced. To a considerable degree this was due to a shift of emphasis in the interest of the state. Following the Restoration, and particularly after the revolution of 1688, the focus of governmental interest shifted more and more to commercial and colonial policy, and regulation in relation to these areas of activity. This had important results on the development of social policy, and on the evolution of ideas concerning the social relations of health.

As the control of the Crown relaxed, local government in the course of the eighteenth century became increasingly a matter of local initiative. In England, local government was carried on by the counties, and by the parishes into which the counties were divided. As a result, the county officials, especially the justices of the peace, gained in power and prestige. It was to the justices that the parish authorities were accountable.[32] There was very little explicit theorizing about this trend of development, but it is clearly reflected in the treatment of social problems, and provides the frame of reference within which thought and action in matters of health must be viewed. Indeed, the outstanding

feature of internal English administration during the period from the Act of Settlement and Removal, passed in 1662, to the Poor Law Amendment Act of 1834 is its intensely parochial character. As a result, England was deprived of any uniform social policy, since there was no machinery to subordinate the interests of the parish to the welfare of the larger community.

During the earlier part of this period, ideas, proposals and programs relating to the social aspects of health took as points of departure either the responsibility of the parish in relieving the needs of the poor, or the desire to increase national wealth by employing the destitute in manufacture. The Elizabethan Poor Law had provided that the parish would carry out the "necessary Relief of the lame, impotent, old, blind and such other among them . . . not able to work," and in time the scope of this provision came to include medical care. Such provision for the sick meant that the parish had to assume considerable responsibilities. However, the parish officers generally had neither training nor desire to engage in such activities. This situation gave rise in parochial administration to the common practice of contracting with private persons to perform public tasks. This system of "contracting" or "farming out the poor" became a typical feature of English Poor Law administration in the eighteenth century. Following this general pattern, parish officers often contracted with a local practitioner for medical treatment of their poor.[33] These contracts varied from parish to parish. Sometimes, the medical practitioner contracted to attend all the poor living in the parish, or only those for whom the parish was legally responsible, and to supply medicine as well. Occasionally, a separate agreement was made with an apothecary. Other contracts exempted such items as smallpox inoculation or epidemic diseases. Some parishes paid per-head, others on a fee for service basis. The practice of farming out public functions such as poor relief became popular because it was regarded as offering an opportunity for reducing taxes. A system of this kind was bound to lead to abuses. Nevertheless, it must be recognized that medical care of a sort was provided, and that the pattern of administration developed in this area had an influence in shaping later schemes for the provision of medical care.

Nonetheless, little attention was given to this subject by contemporary writers and theorists. Such ideas as were developed concerning social problems of health arose rather out of another aspect of the

problem of the poor, namely, the desire to put the poor to work. The problem of the laboring poor, concretely symbolized in the figure of the pauper, occupied a strategic position in the social logic of the eighteenth century. It must be recognized, however, that the category of the "poor" was a broad one, practically synonymous with the "common people." Generally speaking, the "poor" meant all the people who were actually in need, as well as all those potentially eligible for this unenviable distinction.

Behind this concern with the laboring poor were several distinctive motivations. Each parish was responsible for the maintenance of its own poor, and consequently was concerned to reduce this burden as far as possible. It was felt that this might be accomplished by making arrangements to employ the poor. At the same time, this approach was in keeping with the contemporary desire to stimulate national prosperity by using the unemployed poor in manufactures. England at this time was entering upon the path toward industrialism, and the proponents of this view believed that the poor could provide an easily available labor force for the expansion of industry. Between the Restoration and the end of the eighteenth century scores of books and pamphlets were written on this subject, and many projects were suggested to deal with the problem. These proposals, as well as the optimism and eagerness with which they were put forth are characteristic of the tendency of the period to indulge in projects. This tendency is perhaps best described in the words of Daniel Defoe. "Necessity, which is allowed to be the mother of invention," he wrote in 1697, "has so violently agitated the wits of men at this time, that it seems not at all improper, by way of distinction, to call it the Projecting Age. For though in times of war and public confusions the like humour of invention has seemed to stir, yet, without being partial to the present, it is, I think, no injury to say the past ages have never come up to the degree of projecting and inventing, as it refers to matters of negoce, and methods of civil polity, which we see this age arrived to."[34]

The avowed aim of the projectors was to create centers of manufacture in the form of workhouses where the poor could learn to support themselves. This idea did not actually become popular until the end of the seventeenth century, when a corporation for the relief and employment of the poor was established by act of Parliament at Bristol in 1696. Here all the parishes of the town were combined into a single

unit. This experiment developed out of a frank recognition that the individual parish was too small a unit to provide remunerative employment for the poor.[35] The example set by Bristol was soon followed by other towns, and during the earlier eighteenth century there was a steady increase in the number of workhouses. It is of interest to note that while the Board of Trade was considering the problem of pauperism, John Locke, the philosopher, then a member of the Board, proposed a nation-wide system of workhouses.[36] The Bristol experiment probably influenced Locke, particularly since he was a friend of John Cary, its leading proponent.

While the enthusiastic belief in the efficacy of workhouses to deal with poverty was never realized, plans and programs for coping with the health problems of the poor were developed and some of these were even put into practice. Closest to the prevailing parochial pattern was the mode of providing medical care for the sick poor at Bristol. "To such as were sick," stated Carey, "we gave warrants to our physician to visit them; such as wanted the assistance of our surgeons were directed to them, and all were relieved till they were able to work; by which means the Poor, having been well attended, were set at work again, who by neglect might with their families, have been chargeable to the corporation."[37]

More imaginative, immeasurably broader in scope, and based on considerable insight into the socio-economic aspects of health was the plan proposed by John Bellers in 1714.[38] Bellers (1654-1725) was a Quaker cloth merchant of London who around 1679 began to carry on philanthropic work to improve the lives of the poor. Toward this end, he put forward a number of proposals, verbally and in books. Best known of these is his *Proposals for Raising a Colledge of Industry of all useful Trades and Husbandry* . . . which first appeared in 1695. In 1710, Bellers published *Some Reasons for an European State* . . ., presenting in essence a plan for a supranational organization like the League of Nations or the United Nations.

In 1714, Bellers published a treatise in which he set forth a plan for a national health service. This is the substance of his *Essay Towards the Improvement of Physick. In Twelve Proposals. By which the Lives of many Thousand of the Rich, as well as of the Poor, may be Saved Yearly. With an Essay for Imploying the Able Poor, by which the Riches of the Kingdom may be greatly Increased; Humbly Dedicated*

to the Parliament of Great Britain.

The substance of Beller's argument and proposals may be summed up as follows: Illness and untimely death are a waste of human life. The health of the people is extremely important to the community so that it cannot be left to the uncertainty of individual initiative, which the high incidence of curable disease shows to be inadequate to the task of dealing with this social problem. On these grounds Bellers proposed the establishment of hospitals and laboratories to be used as teaching and research centers, the erection of a national health institute, and the provision of medical care to the sick poor.

While the full potentialities of this remarkable plan were to remain unrealized for over two centuries, there was an increasing recognition in Britain during the eighteenth century of the need for medical assistance to certain groups in the population. It was this period, particularly the years from 1714 to 1790, which witnessed the creation of dispensaries, general hospitals in London and the provinces, and hospitals for special groups of patients. The dispensary movement as well as the hospital movement found their impetus chiefly in private initiative and contributions, although there was some governmental assistance in the form of legislative action. This development of private initiative coupled with cooperative action is characteristic of Britain in the eighteenth century. To a very considerable degree this phenomenon is related to the limited character of local governmental activity. In many ways, this very aspect of the governmental system gave increasingly greater scope to private initiative, making it necessary and possible to deal on an empirical basis with new problems as they presented themselves. Indeed, throughout this period Parliamentary action was generally undertaken on the basis of previously established local programs and projects. Out of such activities there gradually emerged a theory of social action in relation to health. This "New Philosophy," as it was called by Sir Thomas Bernard, may be considered the British counterpart of the continental concept of medical police.[39] While not as systematically developed, it was an accurate reflection of the activities carried on by physicians and laymen. In fact, the "New Philosophy" did for the area of health and social welfare what Adam Smith achieved contemporaneously for economic organization. It provided a theoretical formulation of the consequences which men had already drawn practically from the new social order. But it was during the seventeenth century that

the basis of this order was created. In retrospect, it is clear that English social policy in relation to medical care first began to take modern form in the seminal seventeenth century.

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ARTURO CASTIGLIONI, M.D.

1874 — 1953

Shortly after dawn on Wednesday morning January 21, 1953, Professor Arturo Castiglioni, a fellow member of The New York Academy of Medicine, died in Milan, Italy, at 78 years of age. The shock of his wife's death early in the preceding month of December had profoundly depressed him and his own physical condition deteriorated rapidly thereafter. He repeated frequently that he had already "packed his bags for the Beyond," and efforts of his friends and students to arouse his interest in his beloved studies failed for the first time in more than fifty years. His last public address, "Medicine of the Past and Present," was delivered before an overflowing audience at the Manzoni Theatre in Milan on December 1, the afternoon before his wife's death.

Dr. Castiglioni will be mourned throughout the world, and especially by his students and colleagues in America as well as in his own country of Italy. A great historian of medicine, whose humanistic and philosophical sweep of mind was matched by his careful accuracy of detail, his buoyant spirit will be missed by all who had the joy and privilege of knowing him. His first lectures abroad were given in South America in 1930, at the Universities of Sao Paulo, Rio de Janeiro, Buenos Aires and Santiago. In 1933 he was the Hideyo Noguchi Lecturer at Johns Hopkins University, and the same year lectured at the Academy of Medicine and Columbia University in New York and at universities and medical societies throughout the country. The following year he was Lecturer at the Royal Society of Medicine in London.

Born in Trieste on April 10, 1874, Dr. Castiglioni took his M.D. degree at the University of Vienna in 1896 and worked there on the Clinical Service of Prof. Shroetter until 1898, when he became an intern and then resident physician at the General Hospital in Trieste until 1904. For many years he combined with his studies and teaching of the history of medicine an active practice of his profession as Head of the Sanitary Service of the Austrian Lloyd (1899-1918) and the Lloyd Triestino and Italian Lines (1918-1938). His first teaching position was as Associate Professor of the History of Medicine at the University of Siena in 1921. He held the Professorship of the History of Medicine at the University of Padua from 1922 to 1938, and from 1924 to 1938 was also Professor of the History of Science at the University for Foreigners at Perugia, where he returned after his American sojourn to give a series of lectures each Fall from 1948 to 1952.

During his stay in the United States, Dr. Castiglioni was Research Associate and Lecturer in the History of Medicine at Yale University from 1939 to 1943 and Professor from 1943 to 1947. As a Fellow of The New York Academy of Medicine, his lectures before the Section on Historical and Cultural Medicine will long be remembered. In 1942 he was President of the New York Society for Medical History. The great honor and affection in which he was held by his American colleagues were expressed at the dinner in celebration of his seventieth birthday held at the Waldorf-Astoria Hotel in New York on April 12, 1944, attended by some two hundred friends who came from near and far to pay tribute to the inspiration he had brought to studies in medical history in this country and to present to him a volume of essays written for the occasion.

Throughout his long life Dr. Castiglioni's writings flowed in a continuous stream from his prolific pen and inexhaustible mind. A bibliography of his writings, covering a multitude of subjects, begins with an article published in Berlin in 1898 and continues through over two hundred items in German, Italian, English and Spanish down to his last magnificent studies on Leonardo da Vinci published in 1952. This list does not include three hundred biographies of physicians and scientists for the *Enciclopedia Italiana*, hundreds of critical reviews of medico-historical

books, nor articles written as correspondent for various Italian and German newspapers. His monumental work, *The History of Medicine*, was first published in Italian in 1927, appeared in revised editions of 1933, 1936 and 1949, and was translated into six languages. His *Adventures of the Mind*, *History of Tuberculosis*, and his splendid studies done for *Ciba Symposia* on the history of the University of Padua, the University of Bologna, the University of Vienna, and the study of anatomy during the Renaissance, are among his outstanding contributions, as well as his work on apothecary jars and his repeated incursions into the realm of the history of medicine and magic.

For many years Dr. Castiglioni was Honorary President of the Società Italiana di Storia delle Scienze Mediche e Naturali and in 1950 was Honorary President of the Italian Group of the International Union of the History of Sciences. The imposing list of his memberships in medical societies throughout the world is too long to include here, but he remained an animating figure at meetings of the Lombard Center of the Academia di Storia dell'Arte Sanitaria in Milan, where he last spoke in November 1952 in commemoration of Benedetto Croce and presented a paper on "Pseudo-Plinian Medicine." His last lecture in an Italian University brilliantly closed Prof. Latronico's course in medical history at the University of Milan when he spoke on May 15, 1952 on "Leonardo as Scientist."

After the death of Sudhoff, Arturo Castiglioni and Henry E. Sigerist became the giants in the field of medical history. The universality of Castiglioni's interests and the multiplicity of his writings bespeak the spirit of Renaissance man, of which he was a modern exemplar in the fullest sense. Simple, direct and endearing in his personal relationships, Arturo Castiglioni's memory will remain fresh in the hearts of his friends, while his work will live forever in the annals of medical history and scholarship, a source of information and inspiration to coming generations.

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Wednesday Evening, May 13, 1953 – 8:30 P.M.

For this final meeting of the year, a unique program has been arranged. Each of the five medical schools of New York City—Columbia University College of Physicians and Surgeons, Cornell University Medical College, New York Medical College, Flower and Fifth Avenue Hospitals, New York University College of Medicine and State University of New York College of Medicine at New York City—has selected a senior student to present a ten-minute paper on his concept of the role of historical and cultural medicine in the education of the medical undergraduate. The deans from these schools will be present to initiate discussion. Since it is anticipated that a large number of students will attend, in addition to the regular members of the Section, a lively, informative and entertaining evening is in prospect.

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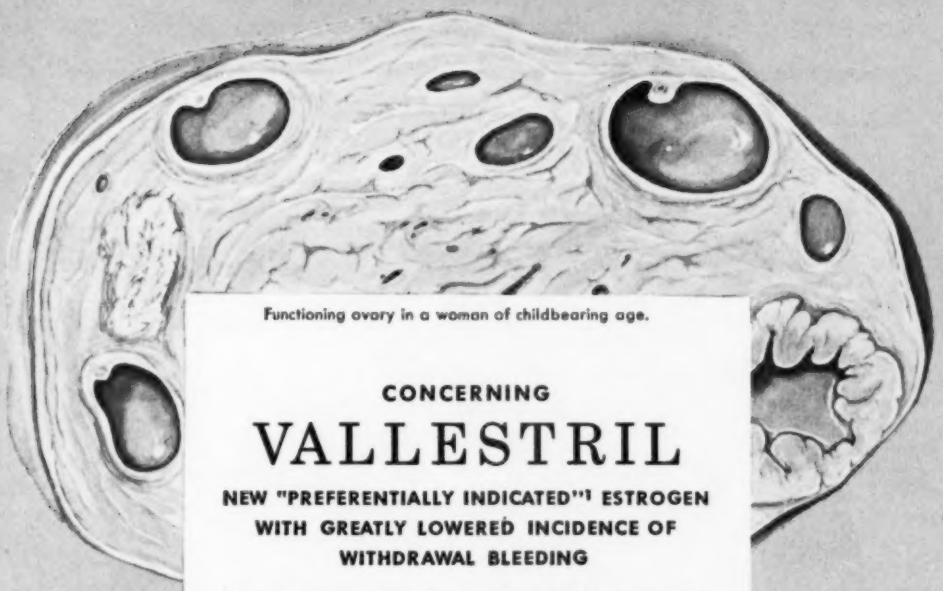

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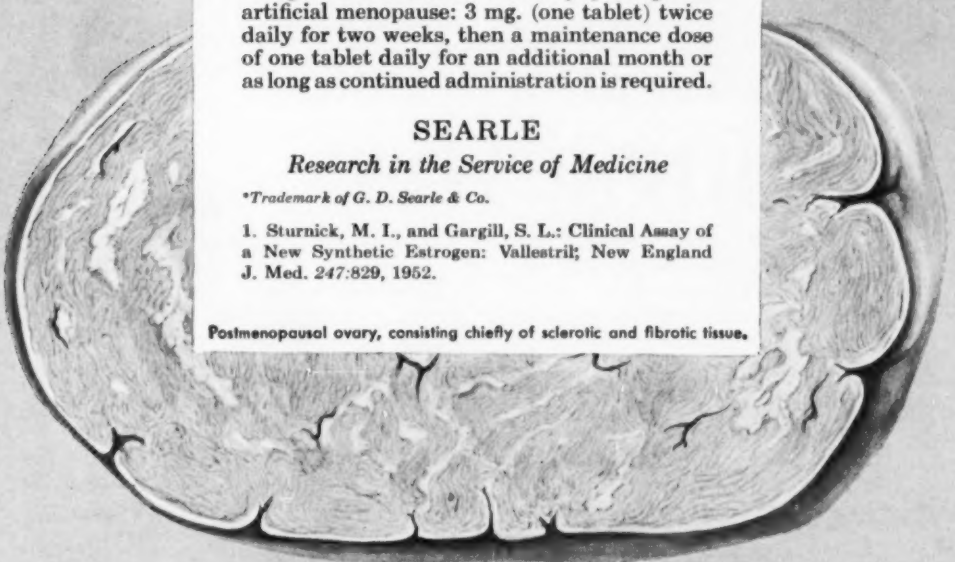
1. Sturnick, M. I., and Gargill, S. L.: Clinical Assay of a New Synthetic Estrogen: Vallestril; New England J. Med. *247*:829, 1952.



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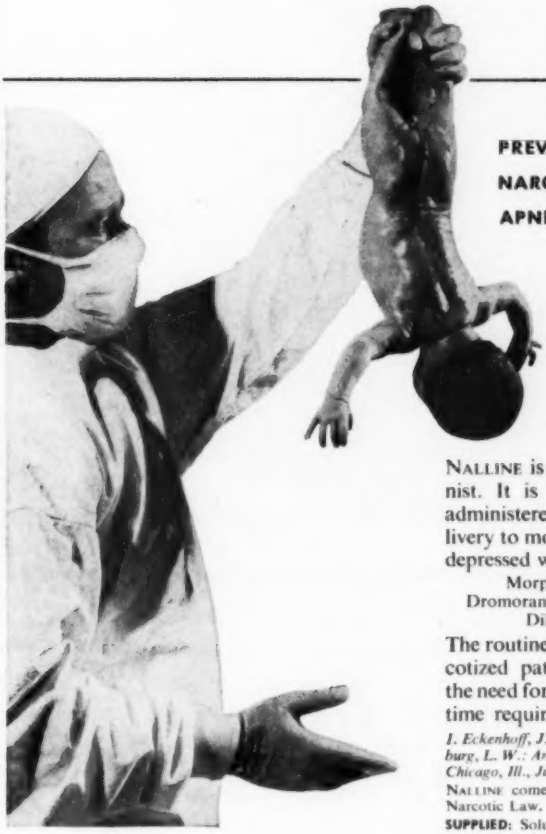

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1. Eckenhoff, J. E., Hoffman, G. L., Jr., and Funderburg, L. W.: American Medical Association Meeting, Chicago, Ill., June 1952.

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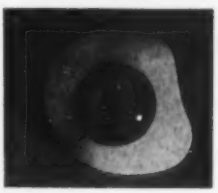

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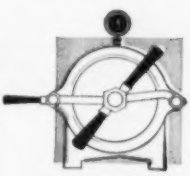

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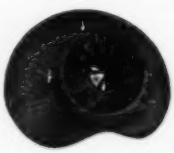

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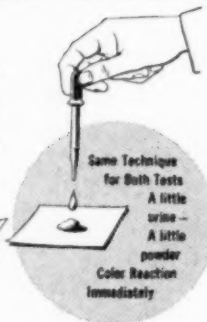

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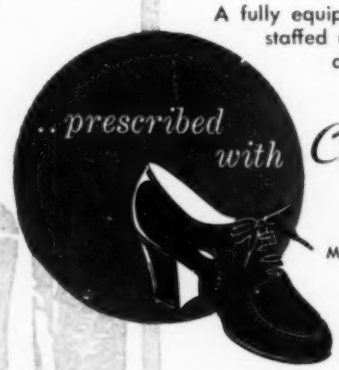

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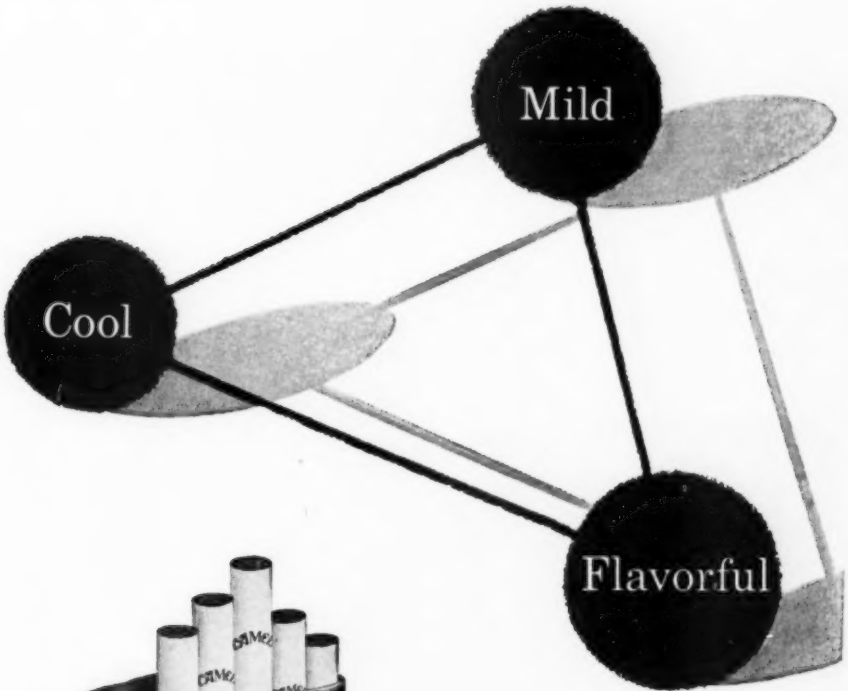

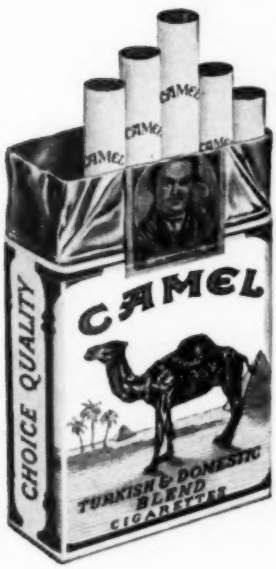

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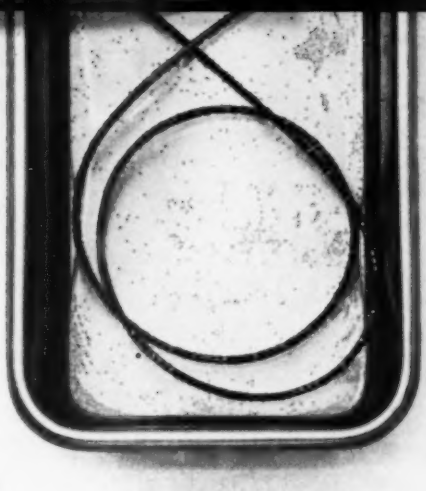
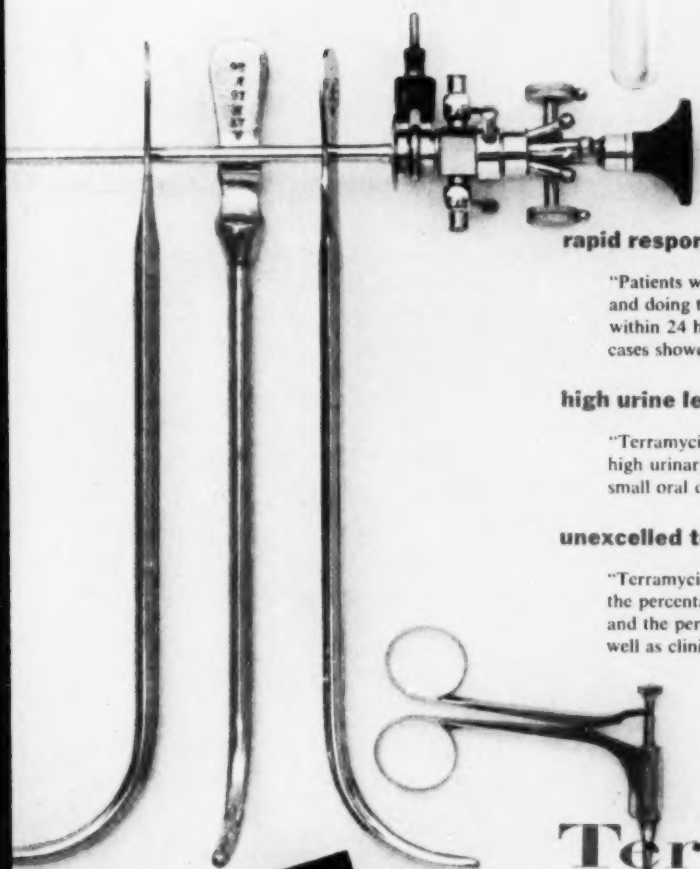


IN URINARY TRACT INFECTIONS



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1. Canad. M. A. J. 66:151 (Feb.) 1952.
2. J. Urol. 67:762 (May) 1952.
3. Ibid. 69:315 (Feb.) 1953.

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